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Coronary artery calcium quantification using contrast-enhanced dual-energy computed tomography scans in comparison with unenhanced single-energy scans

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Abstract

Extracting coronary artery calcium (CAC) scores from contrast-enhanced computed tomography (CT) images using dual-energy (DE) based material decomposition has been shown feasible, mainly through patient studies. However, the quantitative performance of such DE-based CAC scores, particularly per stenosis, is underexamined due to lack of reference standard and repeated scans. In this work we conducted a comprehensive quantitative comparative analysis of CAC scores obtained with DE and compare to conventional unenhanced single-energy (SE) CT scans through phantom studies.

Synthetic vessels filled with iodinated blood mimicking material and containing calcium stenoses of different sizes and densities were scanned with a third generation dual-source CT scanner in a chest phantom using a DE coronary CT angiography protocol with three exposures/CTDIvol: auto-mAs/8mGy (automatic exposure), 160mAs/20mGy and 260mAs/34mGy and 10 repeats. As a control, a set of vessel phantoms without iodine was scanned using a standard SE CAC score protocol (3mGy). Calcium volume, mass and Agatston scores were estimated for each stenosis. For DE dataset, image-based three-material decomposition was applied to remove iodine before scoring. Performance of DE-based calcium scores were analyzed on a per-stenosis level and compared to SE-based scores. There was excellent correlation between the DE- and SE-based scores (correlation coefficient r : 0.92–0.98). Percent bias for the calcium volume and mass scores varied as a function of stenosis size and density for both modalities. Precision (coefficient of variation) improved with larger and denser stenoses for both DE- and SE-based calcium scores. DE-based scores (20 mGy and 34mGy) provided comparable per-stenosis precision to SE-based (3mGy).

Our findings suggest that on a per-stenosis level, DE-based CAC scores from contrast-enhanced CT images can achieve comparable quantification performance to conventional SE-based scores. However, DE-based CAC scoring required more dose compared with SE for high per-stenosis precision so some caution is necessary with clinical DE-based CAC scoring.

Keywords

dual-energy computed tomography; material decomposition; coronary artery calcium score

1. Introduction

Coronary artery disease is the most common type of heart disease and is the leading cause of death in the United States. Coronary artery calcium (CAC) score is considered as the most robust predictor of coronary events in the asymptomatic primary prevention population, particularly in the intermediate-risk cohort. Coronary computed tomography angiography (CCTA) workup is a frequently used comprehensive cardiac computed tomography (CT) exam, which is composed of two acquisitions: an unenhanced and a contrast enhanced acquisition. In CCTA, CAC is detected and quantified using the unenhanced CT images. Recent advances in dual-energy (DE) CT scanners allow the generation of virtual non-contrast enhanced (VNC) images through iodine removal from contrast enhanced studies based on material decomposition and virtual subtraction of iodine. This may eliminate the need for dedicated unenhanced scans for CAC scoring in the CCTA workup, so that overall radiation dose, image acquisition time, and cost could potentially be reduced.

Several recent studies examined the feasibility of CAC quantification based on iodine-removed images derived from DE CCTA. In 2012, Schwarz et al. compared the calcium volumes of 36 patients from VNC series acquired on a dual-source CT using a DE CCTA protocol and true non-contrast enhanced single-energy (SE) series. They found excellent correlation between DE and SE scans on a *per-patient* (Pearson correlation coefficient $r=0.94$) and *per-vessel* (r between 0.91–0.94 for the three coronary arteries) level. The mean effective radiation dose was 1.1 mSv and 15.8 mSv for the true non-contrast enhanced SE acquisition and DE-based CCTA acquisition respectively. Yamada et al. investigated the same problem with a fast kVp-switching DE CT. They also found excellent correlation ($r=0.88$) between the scores from VNC and SE images. The mean effective dose of DE CCTA was 4.3 mSv (21 patients). Other researchers using the same scanner model reported similar findings. These studies indicated that CAC identification and quantification based on DE CCTA studies may obviate the need for a dedicated CT calcium scoring study. However, these studies only focused on the agreement between DE- and SE-based calcium scores. Since patient data were used, it was challenging to assess the accuracy and precision of the calcium quantification due to lack of ground truth and repeated scans. The analyses were mostly reported on a *per-patient* level whereas the potential performance differences for each stenosis remained unknown. In addition, none of the studies analyzed the impact of size and density of the calcium stenosis. Some relevant work, although not specific to CAC, showed that the accuracy of iodine/calcium decomposition from DE CT scans was limited when iodine/calcium CT attenuation was low and when the vessel size was small.

In this study, we focus on the quantitative performance of CAC scoring using DE-based iodine-removed CT scans from a third-generation dual-source scanner. Specifically, we conducted a phantom study using synthetic iodinated and non-iodinated vessels with calcium deposits of different sizes and densities to assess the accuracy and precision of

calcium scoring with DE CCTA protocols across a range of dose levels. The quantitative performance of the DE-based calcium scores was compared to the gold standard method: SE unenhanced CT exam with filtered-back projection (FBP) reconstruction. In addition, the correlation between the DE-based scores to the SE-based scores were examined. The impact of vessel diameter and the size and density of calcium deposits on CAC scores was also investigated. With these analyses, we aim to learn at which dose level the performance of CAC scoring using contrast-enhanced DE scans is comparable to that of conventional CAC scores obtained from unenhanced SE CT images, and whether these settings may improve clinical practice (e.g., reduce overall patient dose by requiring fewer scans or provide more reliable quantification).

2. Materials and Methods

2.1 Phantom design

Two sets of vessels (four vessels each) were designed in our lab and were custom built (QRM, Möhrendorf, Germany). The *non-iodinated vessel set* contained four vessels, filled with synthetic blood and the *iodinated set* contained four vessels filled with synthetic iodinated blood. Within each vessel set, two vessels (4.0 mm and 4.5 mm lumen diameter) contained three stenoses with the *same calcium hydroxyapatite (HA) concentration* (236 mg/cm³) but *different sizes* (degree of luminal diameter stenosis: 12.5%, 25%, 50%); the other two vessels (4.0 mm and 4.5 mm lumen diameter) contained three stenoses with *different HA concentrations* (102, 236, 382 mg/cm³) but *the same occlusion size* (50%). We refer to them as vessels with *equal-density* and *equal-size* stenoses, respectively. The layouts of the stenoses in the vessels are shown in Fig. 1a. All the materials were in solid form and had the appropriate attenuation properties compared to real iodinated contrast and calcium deposits for the X-ray energy range investigated. The CT numbers for the stenoses constructed with 102, 236, 382 mg/cm³ HA material were 130, 300, and 475 HU at 120kVp, respectively. The iodinated blood material (tissue-equivalent material enriched with iodine) was 304 HU at 120kVp, corresponding to about 11mgI/mL[†]. The blood material was 43 HU at 80–120kVp. The sizes and densities of these stenoses were clinically relevant and relatively challenging (low density and small stenoses were included).

These vessels were placed in a water tank inside of an anthropomorphic cardiac thoracic phantom (QRM, Möhrendorf, Germany) (Fig. 1b). The thorax phantom consisted of synthetic lungs, spine, and soft tissue-equivalent material and had an effective diameter of about 26 cm. A cylindrical hole in which a water tank was placed was positioned in the central heart region. A two-section cylindrical HA insert with HA density 100 and 200 mg/cm³ (QRM, Möhrendorf, Germany) was also placed inside for calibration purposes.

2.2 Imaging protocols

Acquisition—The phantom was scanned with a third-generation dual-source CT scanner (SOMATOM Force, Siemens, Malvern, Pennsylvania, USA). The thorax phantom with the

[†]The HU value of the iodinated blood material was provided by the phantom manufacture. We estimated the iodine concentration using a calibration approach: iodinated solutions of multiple concentration were scanned at 120kVp and a linear line was regressed for the HU and iodine concentration.

non-iodinated vessel set was scanned using an “unenanced”, prospective ECG-triggered CT (simulated heart rate = 60 beat per minute) protocol with the following parameters: collimation: $2 \times 128 \times 0.6$ mm with a z-flying focal spot technique; gantry rotation time: 250 msec; pitch: 0.2; tube current: automatically determined by CareDose Module (CareDose is an automatic axial and longitudinal tube current modulation, denoted as auto-mAs); and tube voltage: 120 kVp. This protocol is the scanner default for coronary calcium scoring and is being used clinically for asymptomatic patients as well as for patients with known coronary disease. We refer to this dataset as the *SE data/scans* in the rest of the article. Ten repeated scans were acquired with random shift in the phantom position along the z direction between each acquisition. Note that the phantom had no cardiac motion. The mean tube current per rotation and CTDIvol of the 10 repeated scans were 10 mAs and 2.75 mGy as reported in the DICOM header. Using a conversion factor of 0.014 and scan length 15.4 cm, the effective dose was approximated as 0.6 mSv, and dose length product (DLP) was about 42.9 mSv-cm.

The thorax phantom with the iodinated vessel set was scanned with a “contrast-enhanced”, prospective ECG triggered CT protocol with the same parameters as the SE scans except for the tube voltages and exposures. The tube voltage was 90 kVp (Tube A) and Sn 150 kVp (150 kVp with tin filter, Tube B). Three different sets of exposures were selected for Tube A: auto-mAs; 160 mAs; 260 mAs. The highest exposure (260 mAs) was the maximum allowed by the scanner for the size of our phantom. The 160 mAs was chosen to have a CTDIvol value in between those from the auto-mAs and 260 mAs settings. For Tube B, the exposure was automatically determined by the scanner. For both SE and DE scans, prospective tube current modulation was applied by default. Table 1 summarizes the mean mAs for Tube A and B and the CTDIvol values reported in the DICOM header for the 10 repeated scans. Note that the mean mAs for Tube A with 160 and 260 mAs imaging protocols were lower than 160 and 260 mAs, due to the prospective tube current modulation. As exposure was proportional to CTDIvol, the auto-mAs scan protocol resulted in approximately 63 mAs scan for this phantom.

Reconstruction—The “unenanced” SE data and the “contrast-enhanced” DE dataset were reconstructed with a 3.0 mm slice thickness (slice increment = 1.5 mm) in a 20cm field of view. The reconstruction matrix size was 512×512 , resulting in an in-plane pixel size of 0.39 mm. The data were reconstructed by FBP with reconstruction kernel Qr36 for SE data and Advanced Modeled Iterative Reconstruction (ADMIRE) with denoising strength 3 (medium) with reconstruction kernel Qr36 for DE dataset.

2.3 Material decomposition and iodine removal in DE dataset

Each pair of DE contrast-enhanced series from Tube A and B were processed with a three-material decomposition approach based on a volume conservation constraint. The data was processed with in-house using Matlab programming (Mathworks, Natick, Massachusetts).

Letting $\hat{\rho}_k$ be the concentration of k th material in the mixture and ρ_k be the concentration (per unit mass) of the k th material in its pure form, one can derive the following system of equations for multi-energy CT measurements based on three basis materials:

$$CT_{\#} = \frac{\hat{\rho}_1}{\rho_1}CT_1 + \frac{\hat{\rho}_2}{\rho_2}CT_2 + \frac{\hat{\rho}_3}{\rho_3}CT_3 + \left(\frac{\hat{\rho}_1}{\rho_1} + \frac{\hat{\rho}_2}{\rho_2} + \frac{\hat{\rho}_3}{\rho_3} - 1 \right) \times 1000, \quad (1)$$

where $CT_{\#}$ is the CT number of a mixture, and CT_k ($k = 1, 2, 3$) is the CT number of the k th basis material.

Let f_k be the volume fraction of k th material. For a DE system, with a volume constraint assumption, we can further derive

$$\begin{bmatrix} CT_1^L & CT_2^L & CT_3^L \\ CT_1^H & CT_2^H & CT_3^H \\ 1 & 1 & 1 \end{bmatrix} \begin{bmatrix} f_1 \\ f_2 \\ f_3 \end{bmatrix} = \begin{bmatrix} CT^L \\ CT^H \\ 1 \end{bmatrix}, \quad (2)$$

where CT_k^L and CT_k^H represent the CT number of k th material for lower and higher energy scans, respectively. For our application, we selected calcium (HA), iodinated contrast agent, and soft tissue as the three basis materials because our aim was to classify pixels as calcification (HA + soft tissue) or iodinated blood (contrast agent + soft tissue). Our classification was based on whichever class yielded smaller residual. In other words, we assumed f_1 (HA) or f_2 (contrast agent) was 0 and solved for the other two materials. We classified a pixel contained HA if $f_2 = 0$ yielded smaller residual (2-norm), and vice versa. A separation line on the HU plane of the dual-energy images (HU values of low-energy image against high-energy image) was derived analytically to classify each pixel either as iodinated blood or calcification without the need to explicitly calculate volume fraction, f_k .

Specifically, the slope of the separation line was $\frac{p_1 + p_2}{(1 - p_1) + (1 - p_2)}$ where

$$p_k = \frac{CT_k^L - CT_3^L}{CT_k^L + CT_k^H - CT_3^L - CT_3^H}, \quad (k = 1, 2).$$

For calcium scoring, the image sets from Tube A and B were first linearly blended using a ratio of 0.6 (0.6 Tube A + 0.4 Tube B) to form one image set that had CT numbers close to that from the 120 kVp single-energy acquisition. The pixels in these DE-derived linear-blended images classified as iodinated blood were then set to a blood-similar value of 43 HU. We refer to this final image set as the DE-based iodine-removed dataset. Note that for our application, because only pixels with HU values above a certain threshold at 120kVp were considered as calcification, classification was only applied to pixels above the threshold in the blended image. Fig.2 illustrates the classification and iodine-removal process (with threshold = 130 HU).

In practice, the matrix in equation (2) was empirically obtained using several calibration HA cylindrical inserts (diameter: 20 mm, height: 15 mm) with HA density 100, 200, 400 mg/cm³ (QRM, Möhrendorf, Germany) and in-house iodine phantoms with known

concentrations of 2.5, 5 and 10 mgI/ml. The iodine phantoms were made by diluting iodinated contrast agent (Visipaque 320, GE, Princeton, NJ). Visipaque 320 is an iodinated contrast agent that contains 320 mg of iodine per mL. CT scans of each HA or iodine phantom yielded an equation for CT_k^L and CT_k^H . These equations were solved using a least squares method and we determined that for HA, $CT_1^L, CT_1^H = 4924, 2677$ HU and for contrast agent, $CT_2^L, CT_2^H = 10860, 3604$ HU. For soft tissue, CT_2^L, CT_2^H were set as 43 HU, the same as the material used in the vessel phantom. The slope of the separation line was equal to 2.3. Note that these numbers are dependent on scanning conditions. Fig. 3 shows an example of classification on test samples (iodine solutions) and additional tests for the HA phantoms (not shown) yielded similar accuracy.

2.4 Calcium scoring and reference standard

For each stenosis, calcium volume, mass, and Agatston scores were estimated for the SE dataset and the DE-based iodine-removed dataset. All scores were obtained using an in-house automated threshold-based segmentation algorithm, developed using definitions given in McCollough et al. For completeness, we summarized the definitions for each type of scores. For 120 kVp single-energy scan, the Agatston score is based on the product of weighted density score given the highest attenuation value and the area of the calcification, defined as Agatston score = $\sum (w_i \cdot A_i)$, where the weighting factor for slice i ,

$$w_i = \begin{cases} 1, & D_i \in [130, 200) \\ 2, & D_i \in [200, 300) \\ 3, & D_i \in [300, 400) \\ 4, & D_i \geq 400HU \end{cases}$$

where D_i is the peak HU of the calcification and A_i is the area of the calcification at the i th slice. Calcium volume score (in mm^3) was defined as $N_{\text{vox}} \cdot V_{\text{vox}}$ where N_{vox} is the number of calcification voxels and V_{vox} is the volume of each voxel. Agatston score is the most widely used metric for stratify patient into risk groups: on a patient level, Agatston scores of 0, 1–10, 11–100, 101–400, 400+ correspond to no evidence of coronary artery disease, minimal, mild, moderate, and severe risk, respectively. Let the density and measured CT number of the HA calibration insert (Fig. 1b) be ρ_{HA}, CT_{HA} . Let the measure CT number of water be CT_w . The calcium mass score (in mg) was estimated as the sum of the mass scores for all calcification pixels (m_i), where each $m_i = c \cdot CT_i \cdot V_{\text{vox}}$ where c was a calibration factor that equals to $\frac{\rho_{HA}}{CT_{HA} - CT_w}$.

For SE images at 120 kVp, calcifications were identified when the CT value of pixels within the vessel was above a standard threshold of 130 HU and by ignoring structures with size of 4 connected pixels to reduce the influence of image noise in the evaluation. When calculating Agatston score, thresholds of 200, 300 and 400 HU were also used for determining the weighting factors. Although the CT numbers in the SE images at 120 kVp and the DE-derived linear-blended images were close, there were material- and

concentration-dependent differences. Therefore, for calculating DE-based calcium score, the thresholds applied to the DE-based iodine-removed images needed to be calibrated. Since the CT number of HA is proportional to its concentration, there is a linear relationship between the CT numbers of the calcium pixels in the SE image and the linear-blended image. Thus, we determined this linear relationship using HA phantoms of 100, 200, 400 mg/cm³ (QRM, Möhrendorf, Germany). Based on the line obtained after linear regression, calcium pixels of 130, 200, 300, 400 HU in SE images were determined to be 132, 203, 304, 406 HU in the DE linear-blended images. These values served as the thresholds for calculating calcium scores in the DE-based iodine-removed images.

Each stenosis was also scanned using a high-resolution micro CT (Scanco100 Medical μ CT, Scanco USA, Wayne, Pennsylvania, USA) at 70 kVp and reconstructed with voxel size of 14.8 micron (isotropic). The reference standard for volume of each calcium deposit was obtained using the semi-automated segmentation tool supplied as part of the micro CT workstation. The reference standard for mass was then calculated as volume $\times$ HA concentration (provided by QRM). No reference standard was evaluated for Agatston score since it does not correspond to a specific physical measurement of the objects. Note that there was no ambiguity differentiating calcium from iodine for the iodinated vessel set due to the low kVp and high resolution imaging settings utilized by micro CT. Table 2 gives the per-stenosis reference standard derived from microCT segmentation and phantom compositional information.

2.5 Image analysis

Image noise was calculated as the standard deviation for a region of interest (ROI size 81 $\times$ 81, about 1000 mm²) of water around the center location in the tank. The effectiveness of iodine removal was assessed qualitatively via visual inspection in a reader study to identify the cases with poor iodine removal. Two trained research staff visually assessed if iodine removal was acceptable for each stenosis for each imaging condition. Calcification maps from the iodine-removed images of each vessel, together with its corresponding ground truth were presented in random order to readers for evaluation. The readers were blinded to the imaging protocol. If there was substantial misclassification for both calcium and iodine, the iodine removal was considered unacceptable. Otherwise, it was considered acceptable. The percentage of unacceptable cases and the percent agreement between the two readers for each stenosis at each imaging protocol were reported.

2.6 Statistical analyses

Accuracy and precision of the calcium score measurements, on a stenosis-level, were evaluated as the percent bias (PB) and the coefficient of variation (CV). PB of volume/mass score was defined as the mean percent error with respect to the micro CT reference standard. CVs were estimated for volume, mass, and Agatston score as the ratio of the standard deviation of scores to their mean value. The 95% confidence interval (CI), estimated via bootstrapping, of each CV of DE and SE were compared to determine if they were significantly different. Two-way ANOVA was applied on 1) vessels with equal-density stenoses to investigate the impact of stenosis size and vessel size; and 2) vessels with equal-size stenoses to investigate the impact of stenosis density and vessel size. Correlations

between DE- and SE-based scores were expressed using the Pearson product-moment correlation coefficient, r . Since we had 10 repeated scans, 10 calcium volume/mass/Agatston scores were obtained for each of the 12 stenoses. Hence, we evaluated the distribution of correlation coefficients using the following procedure: 1) select one SE score and one DE score randomly from the 10 corresponding scores for each stenosis to form 12 pairs of SE- and DE-based scores (one pair per stenosis); 2) calculate the correlation coefficient among these twelve pairs of measurements; 3) repeat step 1 and 2 100,000 times to form the distribution and calculate the mean correlation coefficients and 95% CI.

3 Results

3.1 CT images

Ten series of unenhanced image volumes with SE imaging protocol and 30 series of contrast enhanced image volumes with the three DE imaging protocols as described above were obtained. Fig. 4(a) shows an example SE image and (b-d) shows example DE images at similar location in the z direction. The noise levels were 19.1 ± 0.8 HU for the SE scans and 6.1 ± 0.2 (auto-mAs), 3.8 ± 0.2 (160 mAs) and 3.1 ± 0.2 (260 mAs) for the DE scans. Fig. 5 shows the iodine-removed images from the same location as Fig. 4(b), across the three DE imaging protocols. One can see that the iodine removal quality degrades with increasing noise.

3.2 Iodine removal quality

Fig. 6 gives examples of acceptable and unacceptable cases of iodine removal. There was good agreement between the two readers (mean percentage of agreement 93.3% (70%–100%) for each stenosis and imaging protocol). The acceptance rate for the iodine removal was higher with increasing dose and it was dependent on the size and density of each stenosis in general. The average acceptance rates from the two readers for each stenosis are tabulated in Table 3. For the DE protocol with 260 mAs exposure, almost every stenosis reached 100% acceptance for iodine removal quality. The 160 mAs DE protocol also performed well, with a minimum of 90% acceptance. The iodine removal quality for the auto-mAs DE protocol was substantially worse for all stenoses except the 382 mg/cm^3 stenosis with a size of 50%.

We included all results in the statistical analyses described in Section 3.3–3.4 for completeness. However, a calcium score can still be close to the reference standard even when iodine removal quality is poor because missed calcium pixels might be compensated by misclassified iodine pixels (iodine pixels classified as calcification). Therefore, caution should be used when interpreting results which in a large number of cases with unacceptable iodine removal quality (e.g., protocols where the percentage of acceptable iodine removal cases is $< 90\%$ in Table 2).

3.3 Calcium quantification accuracy and precision Percent bias and coefficient of variation

Fig. 7 shows PB for volume and mass scores on a *per-stenosis* level for the 4 mm vessel. The trend and values were similar for the 4.5 mm vessel (not shown). For calcium volume scores,

PBs were between -75% to 38% for DE protocols and between -97% to 38% for SE protocol. For mass scores, PBs were between -84% to -4% for the DE protocols and between -98% to -18% for SE protocol.

Table 4 shows CVs for Agatston scores. For SE, CVs for the relatively large and high density stenoses (size = 50% and HA density = 236 mg/cm³) ranged between 0.02 and 0.07 and for the other stenoses ranged between 0.17 and 3.16. Agatston scores derived from SE dataset and high exposure (260 mAs) DE dataset had comparable precision with only one DE protocol CV (for 382 mg/cm³ stenosis, 4 mm vessel, CV 0.05 versus 0.02) significantly greater than the SE results as shown in Table 4. The differences in CV (DE - SE) were between -0.03 and 0.05 for the large and high density stenoses and less than 0.09 for the other stenoses. The 160 mAs DE protocol performed similarly, with only 2 CVs significantly greater than that from SE. The differences in CV (160 mAs DE - SE) were less than 0.08 for the large and high density stenoses and less than 0.32 for the other stenoses. The auto-mAs DE protocol showed substantially more variability across stenoses and performed worse than SE in general. The trends and values were also similar for calcium volume scores and mass scores (not shown).

Impact of vessel diameter, stenosis size, and density—The importance of size and density of stenoses on the accuracy of calcium quantification were supported by two-way ANOVA analyses. For the vessels with equal-density stenoses, two-way ANOVA for each type of calcium scores with each of the three DE protocols showed, stenosis size, vessel diameter, and their interaction were statistically significant factors. Similarly, for the vessels with equal-size stenoses, stenosis density, vessel diameter, and their interaction were significant effects for volume, mass, and Agatston scores for all protocols. Table 6 shows two representative ANOVA tables.

3.4 Correlation with unenhanced SE scan

Comparing volume, mass, and Agatston scores for the non-iodinated vessels scanned with the SE protocol to the iodinated vessels scanned using DE protocols, Pearson's correlation coefficients, *r*, showed high correlations ranging from 0.92 to 0.98 (Table 7).

4. Discussion

In this work, we investigated the performance of calcium scoring using scans derived from DE CCTA protocols. We qualitatively evaluated the iodine removal quality, and quantitatively evaluated the accuracy and precision of the calcium scores. Three DE protocols were examined, with about 8 mGy (auto-mAs: ~63 mAs), 20 mGy (160 mAs), and 34 mGy (260 mAs). Iodine removal from DE protocols with 160 mAs and 260 mAs exposure, which results in relatively high doses, was found acceptable by the participants in our reader study, achieving at least a 90% acceptance rate for all the stenoses. With auto-mAs, the iodine removal quality was degraded such that a number of unacceptable cases were identified by the readers (average acceptance rate ~65%).

The accuracy of quantifying individual HA stenoses was highly dependent on the property of the stenosis with similar trends for DE and SE as shown in Fig. 1. Small (12.5% and

25%) and low HA density (236 mg/cm³ HA or lower) stenoses were underestimated and high density stenoses tended to be overestimated. There are multiple reasons for the measurement error. Limited spatial resolution of the CT system and partial volume averaging were the main challenges for measurement accuracy. For DE, there were also errors associated with the misclassification of iodine/calcium pixels due to noise and partial volume effects. The precision, quantified by the CVs for calcium scores, improved with larger occlusion and stenoses with higher HA density (Table 4). While we were able to assess stenosis-based accuracy and precision in our phantom study, the aforementioned studies in Section 1 did not include these analyses as they were based on patient data and had no repeated scans. – These earlier studies mainly examined the correlation coefficients between SE and DE results, as the conventional approach for characterizing cardiac risk is based on Agatston scores from true unenhanced SE scan. Therefore, we also examined the correlation and the results were comparable to those reported in the literature.

Regarding the radiation dose, earlier studies suggested that the dose for the contrast-enhanced DE acquisition alone was less than unenhanced and enhanced SE acquisitions combined. From our study, we see the need of using CTDIvol of at least 20 mGy (DE 160 mAs) with iterative reconstruction (ADMIRE) to achieve high iodine removal quality and *per-stenosis* accuracy and precision comparable to that of the SE protocol. This amount of radiation dose (20 mGy CTDIvol) generally exceeds the dose of an unenhanced scan for CAC combined with a contrast contrast-enhanced scan in SE mode, which have dose of 2.75 mGy and 8 mGy, respectively. Hence, DE CCTA may not be advantageous over the current conventional approach (SE CAC + SE CCTA) in terms of potentially saving overall patient dose if assessment of individual per-stenosis calcification is required.

However, it is the summation of the stenoses scores that determines the coronary artery disease risk category for a patient in clinical practice. As introduced earlier, Agatston scores of 0, 1–10, 11–100, 101–400, 400+ correspond to patients with no evidence of coronary artery disease, minimal, mild, moderate, and severe risk. To investigate how consistent DE-based Agatston scores are compared to SE-based Agatston score in terms of risk category prediction, we compared the Agatston score based risk categorization for each individual stenosis, each vessel (summation of three stenoses), and all vessels together (summation of 12 stenoses) (Fig.8, Table A1). There was good agreement in risk categorization except for small, low density individual stenoses that are associated with the low risk categorization. This is likely because the range in the low risk categorization was relatively small such that minimal uncertainty is allowed for the no evidence of coronary artery disease group and minimal risk categories. For these two categories, even SE-derived scores among repeats did not agree all the time. Therefore, the overall risk categorization using the DE CCTA protocol even with low CTDIvol may be comparable to SE protocol for patients, especially those with higher risk of coronary artery disease. Thus, DE-based CAC scoring is feasible and potentially beneficial for this population by eliminating the need for the unenhanced CT scan and reducing radiation dose. For asymptomatic patients, SE- and DE-based risk stratification are more likely to differ as they are associated with lower risk (the calcium scores tend to be based on smaller/less dense stenoses) on average. Therefore, conventional SE scan should remain the method of choice for asymptomatic patients since the

effectiveness of SE-based CAC quantification has been extensively established for this population.

We should point out that this study has limitations. (1) Unlike most of the studies performed on patients in the literature, we used our own iodine removal tool as presented in section 2.3 instead of using the VNC or iodine removal function on the scanner. The results from the proprietary algorithms for the scanner or other solutions for material deposition (such as projection-based, mass conservation based) may be different. However, our approach is one of the standard approaches in material differentiation and is similar the iodine/bone removal program on the Siemens' Syngo.via – where the users can adjust a parameter called 'ratio' to achieve material differentiation through a separation line. The difficulty with these programs on the Siemens' Syngo.via was that, as far as we know, they were not adjusted specifically for use with coronary angiography data. In addition, while a discussion on the effect of different material decomposition methodologies are beyond the scope of this work, we believe the conclusions from our study are very likely to hold across approaches because the material decomposition method applied in this study yielded reasonable iodine removal quality for most cases. This was confirmed by the results of our reader study. The details of our method provided are also sufficient for others to understand and implement our methods which isn't necessarily the case for the commercial packages. (2) Our study was limited to vessels of 4 mm and 4.5 mm in lumen diameter. These two vessel sizes were selected because they corresponded to the average sizes of left main artery in an average women and man. The reason we did not include smaller vessels was because a previous study showed difficulty in quantifying calcified stenoses in smaller vessels even in non-contrast enhanced SE scans. Note, we did include smaller stenoses (e.g., the 12.5%, the area stenoses) which are on the same order as image resolution. These smaller stenoses represented, at least in a loose fashion, calcium sizes that could be present in smaller vessels. (3) Only one size was available for the chest phantom and there was no cardiac motion. While fixing the phantom size and excluding motion artifact is a limitation, we are not aware of published studies that investigate the appropriate dose for quantifying coronary calcium scoring using DE CCTA protocol even under the idealized, no motion setting investigated in our study. More importantly, studying the no motion situation allows us to investigate fundamental factors in how dose and characteristics of stenoses impact calcium scoring with DE CCTA protocols precisely because we removed a major source of variability. With cardiac motion, calcium scoring may benefit from DE scans because of its potential in reducing blooming artifact. However, as the temporal resolution of SE protocol (both tube operating at 120kVp) is higher than DE (two tubes operating at different kVp) protocols on a dual-source CT scanner, SE protocol may be favored. This is certainly an area in need of additional investigation.

5. Conclusion

It is feasible to extract calcium scores from contrast-enhanced images using DE-based material decomposition methods such that the need for unenhanced SE scans dedicated to CAC scoring may be eliminated, especially for summed scores of multiple stenoses of different sizes and densities. However, DE-based CAC scoring required more dose compared

with SE for high *per-stenosis* precision so some caution is necessary with clinical DE-based CAC scoring.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix:

List of Abbreviations

Auto-mAs	automatic exposure, tube current time product (mAs) determined by an automatic axial and longitudinal tube current modulation called CareDose (Siemens Medical Solutions USA, Inc, Malvern, PA)
CAC	coronary artery calcium
CCTA	coronary computed tomography angiography
CI	confidence interval
CT	computed tomography
CV	coefficient of variation
DE	dual-energy mode of CT scanner
FBP	filtered-back projection
HA	hydroxyapatite
PB	percent bias
ROI	region of interest
SE	single-energy mode of CT scanner
VNC	virtual non-contrast enhanced

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Fig. 1.

a) The design schematic of vessel phantoms (stenoses denoted by gray area with stripe pattern) and b) the cardiac anthropomorphic thoracic phantom with the four vessel phantoms and the cylindrical HA insert within a water bath placed in the central heart region.

Fig. 2.

Illustration of iodine/calcium classification and iodine removal. Pixels with HU higher than 130 in the linear-blended image ($0.6 \text{ Tube A} + 0.4 \text{ Tube B}$) are classified as iodinated blood (pink region in the HU-plane) or calcification (striped gray region). For the iodine-removed images, HU values of iodinated pixels are assigned as that of soft tissue.

Fig. 3.

The test samples for validation of the iodine-calcification classification algorithm (Iodinated solutions of 2.5, 5, and 10 mgI/ml for samples A-C). Pixels classified as iodine (b) and calcification (c) are masked in red and yellow respectively. Soft tissue corresponds to non-colored pixels. The mean HU for samples A-C in (a) were 76, 142 and 272 HU. For sample A, the mean HU was below the threshold. For sample B and C, >99% and 100% of the pixels were classified as iodine. Part D is the spine insert and it was generally associated with calcification. Window/level: 600/200 HU.

Fig. 4.

(a). An example image for the non-iodinated vessels from an SE scan. The center corresponds to the HA calibration insert (200 mg/cm^3). This slice contains the $[12.5\%, 236 \text{ mg/cm}^3] / [50\%, 382 \text{ mg/cm}^3]$ stenosis for the vessels on the left/right, as indicated. (b). A DE-derived linear-blended image with 260 mAs exposure. This slice also contains stenoses with the same properties as those in (a). (c) and (d) are the images from Tube A and B that were used to create (b). Window/level: 900/250 HU.

Fig. 5.

Iodine-removed images (zoomed in) from each DE imaging protocol at the same z-location as Fig. 4b. Only the center part of the images (10cm×10cm) was shown for a close-up view. From the left, the reference standard image, images of 260, 160, and auto-mAs are shown. With increasing noise, material decomposition quality degrades relative to the reference standard (more pixels misclassified as iodine and assigned as soft tissue pixels (=43HU) within the stenosis and the central HA insert). Window/level: 900/250 HU.

Fig. 6.

Example stenoses with acceptable (a) or unacceptable (c) iodine removal based on reader assessment. Five neighboring slices are shown for each case. Images in (a) and (c) correspond to calcification pixels from the DE scans after iodine removal. (b) and (d) are the calcification ground truth for (b) [50%, 382 mg/cm³] and (d) [12.5%, 236 mg/cm³] stenoses. Window/level: 500/250 HU.

Fig.7.

Percent bias comparison for the 4 mm (a) vessel with equal-size stenoses and (b) vessel with equal-density stenoses. Bars with “#” indicate that the iodine removal quality was not ideal for the corresponding stenosis and imaging protocol (see Table 3, percentage of cases with acceptable iodine removal quality < 90%).

Fig. 8. Plot of SE-, DE-derived Agatston scores for each individual stenosis from the four vessels (a)-(d). SE, DE with 260 mAs, 160 mAs, and auto-mAs results are shown in circle, square, triangle and star (10 repeats for each protocol, jittered for visualization). Points with different color correspond to different risk categorizations. Dashed lines correspond to the thresholds for risk categorization. Plot (e) shows the summed scores for each vessel and the total score (summed scores for all stenoses across all vessels).

Table 1.

Mean (minimum - maximum) tube current per rotation (both tubes) and CTDIvol reported in the DICOM header for the 10 repeated acquisitions using the DE CCTA protocols. Effective dose and DLP are estimated from CTDIvol.

	Tube A/90kVp (mAs)	Tube B/150kVp with Tin filter (mAs)	CTDIvol (A+B) (mGy)	Effective dose (mSv)*	DLP (mSv-cm)*
DE auto-mAs	30.4 (30–31)	28.5 (28–29)	7.96 (7.81–8.07)	1.71 (1.68–1.73)	122 (120–123)
DE 160 mAs	87.4 (86–89)	66.3 (65–69)	20.5 (20.16–21.0)	4.42 (4.35–4.52)	315 (310–323)
DE 260 mAs	142.6 (141–144)	109.6 (106–113)	33.6 (32.8–35.2)	7.24 (7.07–7.59)	517 (505–540)

* : estimated using a conversion factor of 0.014 and scan length 15.4cm

Table 2.

Reference standard of volume and mass for each stenosis.

dataset	Reference standard					
	236 mg/cm ³ (equal-density stenosis)			50% (equal-size stenosis)		
	12.5%	25%	50%	102 mg/cm ³	236 mg/cm ³	382 mg/cm ³
<i>4mm vessel</i>						
Volume (mm ³)	12.2	25.3	65.8	76.9	56.5	67.7
Mass (mg)	2.9	5.9	15.5	7.9	13.3	25.8
<i>4.5mm vessel</i>						
Volume (mm ³)	15.3	28.1	80.4	81.5	71.2	86.0
Mass (mg)	3.6	6.6	19.0	8.3	16.8	32.8

Table 3.

Percentage of cases (across repeats and readers) with acceptable iodine removal quality for each stenosis and imaging protocol. Values $\geq 90\%$ are highlighted in bold.

dataset	Acceptable iodine-removal rate					
	236 mg/cm ³ (equal-density stenosis)			50% (equal-size stenosis)		
	12.5%	25%	50%	102 mg/cm ³	236 mg/cm ³	382 mg/cm ³
<i>4mm vessel</i>						
DE auto-mAs	80%	60%	55%	65%	75%	95%
DE 160 mAs	90%	90%	95%	95%	100%	100%
DE 260 mAs	95%	100%	100%	100%	100%	100%
<i>4.5mm vessel</i>						
DE auto-mAs	40%	30%	50%	65%	65%	95%
DE 160 mAs	90%	90%	90%	100%	100%	100%
DE 260 mAs	95%	100%	100%	100%	100%	100%

Table 4.

Coefficient of variation (CV) of Agatston score for each stenosis for SE and DE protocols with auto-mAs, 160 mAs, and 260 mAs exposure.

dataset	Coefficient of Variation					
	236 mg/cm ³ (equal-density stenosis)			50% (equal-size stenosis)		
	12.5%	25%	50%	102 mg/cm ³	236 mg/cm ³	382 mg/cm ³
<i>4mm vessel</i>						
SE	3.16	0.17	0.07	0.35	0.04	0.02
DE auto-mAs	0.59 [§]	0.33 [†]	0.19 [†]	0.23	0.25 [†]	0.10 [†]
DE 160 mAs	0.60 [§]	0.49 [†]	0.12	0.24	0.06	0.06 [†]
DE 260 mAs	1.30	0.26	0.04	0.21	0.09	0.05 [†]
<i>4.5mm vessel</i>						
SE	2.11	0.21	0.05	0.22	0.05	0.03
DE auto-mAs	0.52 [§]	0.35 [†]	0.12	0.28	0.09	0.07
DE 160 mAs	0.52 [§]	0.12	0.10	0.28	0.13	0.03
DE 260 mAs	0.36 [§]	0.27	0.06	0.27	0.08	0.03

[†] Lower bound of the 95% CI is larger than the upper bound of 95% CI of the corresponding CV for SE

[§] Upper bound of the 95% CI is smaller than the lower bound of 95% CI of the corresponding CV for SE

Table 6.

Two-way ANOVA with interaction for Agatston score with 160 mAs DE protocol. Variables with p -value<0.05 are statistically significant.

(a) Vessels with equal-density stenoses					
Variables	Sum of Squares	Degrees of Freedom	Mean Square	F-value	p -value
A (Vessel Diameter)	2555	1	2555	80.168	<0.001
B (Stenosis Size)	57277	2	28638	943.402	<0.001
AB	1338	2	668	22.036	<0.001
Residual	1639	54	30		
(b) Vessels with equal-size stenoses.					
Variables	Sum of Squares	Degrees of Freedom	Mean Square	F-value	p -value
A (Vessel Diameter)	3223	1	3223	101.243	<0.001
B (Stenosis Density)	140625	2	70312	2208.605	<0.001
AB	1672	2	836	26.262	<0.001
Residual	1718	54	32		

Table 7.

The mean Pearson's correlation coefficient, r , and 95% CI are shown for the three DE protocols (with auto-mAs, 160 mAs and 260 mAs exposure). The correlation coefficients are calculated by correlating the individual DE-based with corresponding SE-based calcium scores (volume, mass, and Agatston scores).

dataset	Score		
	Agatston	Volume (mm ³)	Mass (mg)
DE auto-mAs	0.92 [0.86,0.97]	0.95 [0.91, 0.98]	0.95 [0.91,0.98]
DE 160 mAs	0.96 [0.92, 0.98]	0.97 [0.95, 0.99]	0.97 [0.95, 0.99]
DE 260 mAs	0.96 [0.94, 0.98]	0.98 [0.96, 0.99]	0.97 [0.96, 0.99]