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Coronary artery calcium: A technical argument for a new scoring method

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ABSTRACT

Coronary artery calcium (CAC) is a strong predictor for future cardiovascular events. Traditionally CAC has been quantified using the Agatston score, which was developed in the late 1980s for electron beam tomography (EBT). While EBT has been completely replaced by modern multiple-detector row CT technology, the traditional CAC scoring method by Agatston remains in use, although the literature indicates suboptimal reproducibility and subjects being incorrectly classified. The traditional Agatston scoring method counteracts the technical advances of CT technology, and prevents the use of thinner sections, obtained at lower tube voltage and overall decreased radiation exposure that has become available to other CT applications. Moreover, recent studies have shown that not only the total amount of CAC, but also its density and distribution in the coronary arterial tree may be of prognostic value. Acquisition and reconstruction techniques thus need to be adapted for modern CT technology and optimized for CAC quantification. In this review we describe the technical limitations of the Agatston score followed by our suggestions for developing a new and more robust CAC quantification method.

1. Introduction

Coronary artery disease causes approximately one in every six deaths in the United States, making it the leading cause of death in the US and in other developed countries.[1] Cardiac risk assessment and primary prevention are thus very important. The amount of coronary artery calcium (CAC) is a strong predictor for future cardiovascular events.[2] Clinically, CAC scoring is used to reclassify individuals at intermediate risk into more appropriate risk categories.[3] For example, absence of CAC indicates a subject can be reclassified to low risk, and large amounts of calcium indicate high risk for future cardiac events. Traditionally CAC is quantified using the Agatston score, which can be easily quantified and interpreted within a couple of minutes.[4] While it showed an independent prognostic value in large populations resulting in robust reference score tables, this time-tested method has important limitations.[5] Optimized image acquisition and reconstruction combined with improved quantification can be more robust than traditional Agatston scoring,[6,7] with better reproducibility due to thin-slice reconstructions,[8,9] iterative reconstruction,[10] and improved quantification of low-density calcifications enabled by low tube-voltage acquisitions.[11] This may also result in a reduced radiation dose. These optimizations will most likely improve quantification of zero scores, low positive, or intermediate scores. Moreover, it will allow for evaluation of distribution and shape of calcifications, which may allow refining risk estimates.[12] Machine learning algorithms may be helpful for these evaluations.

2. Image acquisition

2.1. Electron beam tomography

The Agatston score was first published in the early 1990s.[4] At that time the gantry rotation times of mechanically rotating 3rd generation computed tomography (CT) scanners were not fast enough to adequately image a rapidly moving organ, such as the heart. Agatston and colleagues used an electron beam tomography (EBT) system. This scanner had no rotating mechanical elements and with exposure times as short as 50 ms allowed for motionless imaging of the coronary

Abbreviations: CAC, Coronary artery calcium; EBT, Electron beam tomography

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arteries. EBT had limitations pertaining to tube power, slice thickness, and spatial resolution. The X-ray source could only be operated at a single energy level of 130 kVp. Coronary lesions with a density of 130 Hounsfield units (HU) or higher were included in the Agatston score. The area of each calcified lesion (in mm^2) was multiplied by an arbitrary chosen factor related to the peak attenuation: 130–199 HU, factor 1; 200–299 HU, factor 2; 300–399 HU, factor 3; and ≥400 HU, factor 4. The final Agatston score was the weighted sum of scores for all lesions. The most important shortcoming for CAC quantification was the limited through-plane resolution: minimum scan range per heartbeat was 3 mm with the first EBT systems.[13] This resulted in images with 3 mm thick slices, which is large relative to the size of the coronary arteries (the diameter of epicardial coronary arteries ranges from approximately 5 mm proximal to submillimeter and smaller in distal branches). Due to the limited spatial resolution, calcified structures with low density and most lesions with a smaller area than 1 mm^2 could not be detected in the Agatston score. Commonly, Agatston scores are classified into one of the following four risk categories: no (0), mild (1–99), moderate (100–299), or severe (≥300), respectively.[14] These categories result in different preventive measures, therefore changes in these classifications may result in differences in clinical outcome.

2.2. Computed tomography

The evolution of contemporary 3-rd generation CT scanners evolved quickly with the introduction of slip-ring technology and multi-detector CT scanners that combine fast gantry rotation with electrocardiography triggering and dedicated reconstruction algorithms allowing high-resolution volumetric cardiac imaging. The gantry rotation speed of state-of-the-art CT scanners allows a temporal resolution between 65 ms and 130 ms, and coverage of the whole heart within a single or few heartbeats. Modern CT scanners also generate improved image quality at reduced radiation exposure due to optimized detector and image reconstruction technology.[15] Modern detector systems and powerful X-ray tubes and generators of current-generation CT scanners allow the routine acquisition of images with a slice thickness smaller than 1 mm at the isocenter (Fig. 1). Increased tube power reserves also enable imaging at lower than the traditional 120 kVp tube voltages. This enables improved 3-dimensional evaluation of CAC and theoretically allows more precise and robust quantification. Despite these technical advances, the original scoring method for CAC has not been substantially updated since the 1990s.

While several alternative methods to the Agatston scoring method have been proposed,[16,17] none have been incorporated into routine clinical practice or current guidelines, which retain the traditional Agatston score. The Agatston score has been used in all major large cohort studies,[2,3] resulting in an abundance of prognostic data for the Agatston score, and a lack of data for newer, potentially more sensitive, robust, and dose efficient scoring methods.

3. Limitations of the agatston score

3.1. Image acquisition and reconstruction: impact on image quality, noise, and radiation dose

A major limitation of the Agatston score is that it is *not conducive to modern methods of radiation dose reduction* (Table 1). The radiation dose of coronary CT angiography has decreased tremendously over the last years with the use of prospective electrocardiography (ECG) triggering, tube current modulation, low kVp acquisitions, fast (high-pitch) spiral acquisitions, and iterative reconstruction.[18] Radiation doses of CT exams for CAC quantification have also decreased,[19] but to a lesser extend. The most important methods to reduce the CT radiation dose include lowering the voltage (kVp) and current (mA) of the X-ray tube of the CT scanner. While this would result in noisier images if the same mA was used, this can be compensated for by increasing tube current combined with using iterative reconstruction algorithms that reduce image noise.[20,21] Since the Agatston score is based on counting picture elements (pixels), weighted by the peak CT attenuation (in Hounsfield units), any acquisition or reconstruction parameter affecting the dimensions of a pixel (or voxel – volume element; i.e. pixel x section thickness), and any changes affecting the CT attenuation values will alter the Agatston score for a given patient. Iterative reconstruction algorithms, however, should be used with caution since they reduce noise, which affects Agatston scores resulting in misclassification rates ranging from 3% up to 31%.[22–24] Reduced kVp scanning is a powerful dose reduction method but it increases the CT attenuation of calcium. Reduced kVp scanning combined with iterative reconstruction has not been validated in large prospective multicenter trials and impact on patient management and outcomes. The 2017 CAC expert consensus from the Society of Cardiovascular Computed Tomography states that iterative reconstruction combined with 100 kVp acquisition may be used as an alternative to FBP with 120 kVp, however this should be utilized with caution after site-based or literature-based validation for

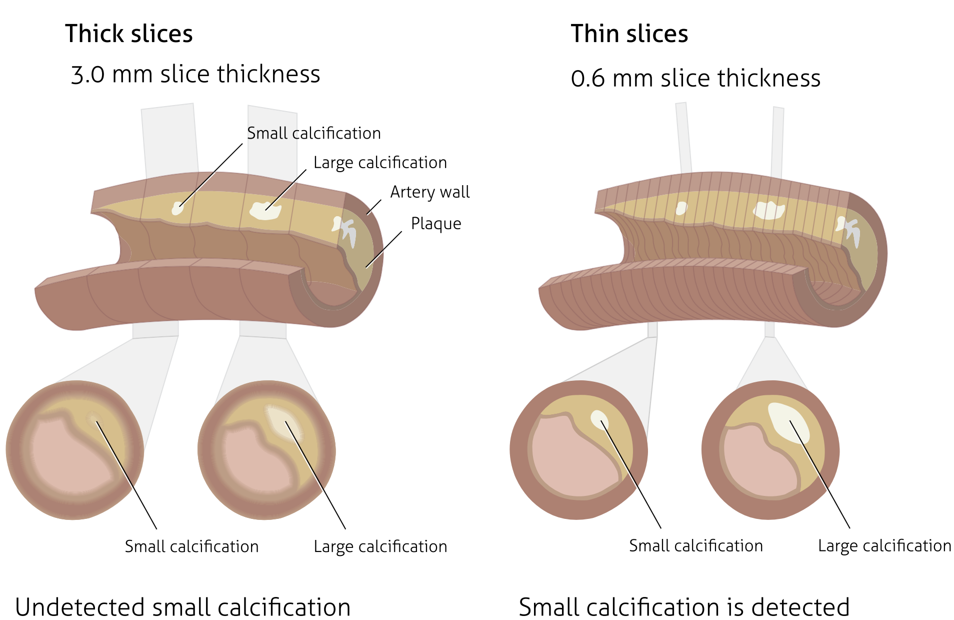

Fig. 1. Partial Volume. Thick slice reconstructions (left) result in blurry images with less detail and small calcifications remain undetected. Thin slice reconstructions (right) result in sharp images with more detail and small calcifications can be detected. This results in more adequate quantification of coronary artery calcium and allows for newer quantification methods such as calcium volume and mass.

Table 1
Factors influencing the Agatston score.

Factor	Disadvantage
Slice thickness (3 mm)	• Small and low-density calcifications may not reach 130 Hounsfield unit threshold due to partial volume effect. • Reproducibility decreases with thicker slices. • Less suitable for 3D volumetric evaluation than thin slice images.
Tube voltage (120 kVp)	• Not as suitable as low kVp imaging for radiation dose reduction. • Detectability of low-density calcifications is reduced compared to low tube voltage imaging.
Peak density within lesion	• Affected by noise. If the noise is high, the maximum attenuation of a lesion increases, whereas the average attenuation stays the same. This prohibits the use of low dose acquisitions and reconstruction of images with thin slices and iterative reconstruction.
Thresholds (130/200/300/400 Hounsfield units)	• Arbitrary chosen and systematic research is needed to find more optimal thresholds.
Summarizing all lesions	• Equal scores for differently located lesions does not allow for evaluation of distribution of calcifications throughout the coronary tree.

each scanner vendor.[14] Early studies on radiation dose reduction mainly evaluated correlation between routinely used radiation dose scans and reduced radiation dose scans and found excellent correlations. However, recent studies have shown misclassification rates ranging from 15% up to 29% after 80% dose reduction.[10,25] This is mainly due to the dependency of the Agatston score on the peak density of calcified plaques, which is substantially influenced by noise, thus resulting in different Agatston scores.

3.2. Sensitivity

The second limitation of the Agatston score is that it is based on a relatively large section thickness (for today's standards) of 3 mm. The resulting *poor spatial resolution*, limits the detection and quantification of small calcifications due to partial volume effects. Smaller and less dense calcifications may be underestimated or completely missed depending on the relative location within a 3 mm thick slice (Fig. 2). We evaluated 1871 clinical CAC CT scans acquired at our institution over the last 5 years (unpublished data). In total 959 scans (51.3%) showed a zero Agatston score. Additional thin slices were routinely reconstructed to evaluate lung parenchyma in the majority of these scans (N = 826/959, 86.1%). Despite zero Agatston scores, we found small coronary calcifications in 118/826 patients (14.3%) on thin slices. This number is similar to a study conducted by Urabe et al., who detected coronary calcifications in 18/132 patients (13.6%) with a zero Agatston score.[26] Aslam and colleagues detected coronary calcifications in 24 patients on 0.5 mm images of 48 patients with a zero Agatston score on 3 mm images.[27] It is currently unclear if the detection of small calcification is prognostically important since current acquisition and reconstruction methods do not allow for evaluation of sub-threshold small calcifications. However, there is a dose-response curve for the quantity of calcium and the occurrence of adverse events. Patients with a low calcium score (1–10) are at higher risk compared to those with zero calcium.[28] While the entire cohort of zero calcium is at low risk, those events that do happen may do so in patients with calcifications just below the threshold of detection. Improved spatial resolution and sensitivity to smaller lesions is also desirable for studying higher order information about calcified plaque: it is very well possible that not only the total amount of coronary calcium, but also the shape and the density of individual lesions, and their distribution within the coronary arterial tree convey additional or modulate prognostic information based on density alone. Another factor that limits the detection and quantification of small and less dense calcifications is the threshold of 130 HU used for CAC quantification. This threshold is arbitrary and systematic research is needed to find a more optimal threshold.

3.3. Reproducibility

While the Agatston score is a successful test since it is relatively easy to obtain, the third limitation is its inherently *suboptimal reproducibility*. Since scoring of individual lesions is based on the maximum pixel attenuation with an arbitrary threshold of 130 HU, the method is vulnerable to image noise and beam hardening. Standard acquisition parameters for modern day CAC scoring across different CT manufacturers were proposed in a consensus paper by McCollough et al., in 2007.[29] Similar CT scanner settings should result in similar Agatston scores. In 2014, however, Willemink and colleagues showed that clinically used vendor recommended CT scanning protocols resulted in substantially different Agatston scores between CT manufacturers.[30] Median Agatston scores of 14 ex-vivo hearts for the CT system with the highest scores were 469.0 (182.8–1381.0) compared to 332.1 (114.3–1134.6) for the CT system with the lowest scores. The median relative difference between the same systems was 43.9 (21.9–55.1). If an individual undergoes a CAC CT scan at one site, he or she could be

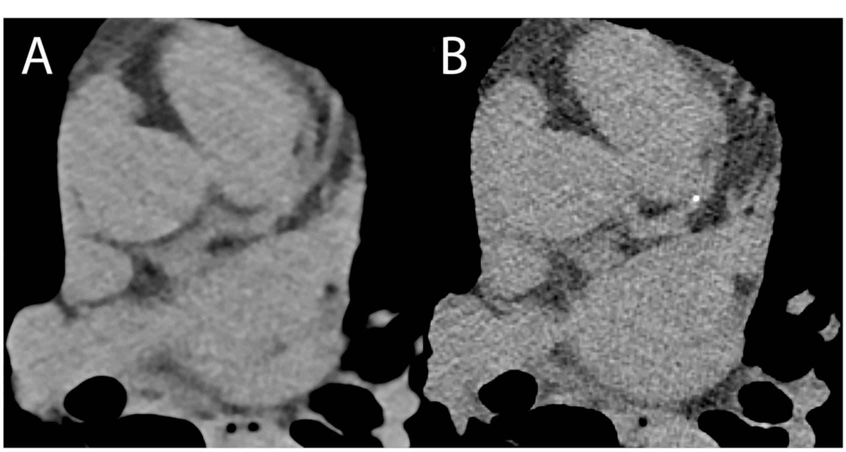

Fig. 2. False-negative Calcium Scores. Calcium scoring CT scan of a 61-year old female acquired with 120 kVp and reconstructed with standard 3 mm slice thickness (A) and 0.6 mm thin slices (B). The calcification proximal in the left anterior descending artery did not reach the 130 Hounsfield unit threshold on the 3 mm image resulting in a false-negative score, while it did reach the threshold on the 0.6 mm image.

classified differently compared to another site with a different CT scanner; this was the case in up to 6.5% of subjects. Treatment recommendations for the same patient could thus differ between sites. Several studies have reported differences in CAC scoring between CT systems[19,30,31] and high inter-scan variability of Agatston scoring.[6,7,32–34] Rutten and colleagues showed that a small variation in patient position in the scanner leads to different Agatston scores with median absolute percentage differences ranging from 147 (0–200) in patients with low Agatston scores (ranging from 1 to 10) to 7 (4–22) in patients with high Agatston scores (> 400).[33] This resulted in potentially misclassification of approximately 10% of patients. The lack of reproducibility is multifactorial including motion artifacts and volume averaging. Another important factor limiting the reproducibility is again the conventional use of 3 mm slices for Agatston scoring. Simply reducing the slice thickness alone, however, will also affect Agatston scores.[8,9,27,35–38] With current acquisition protocols, CAC scores also differ between larger and smaller patients.[39,40] Compared to EBT – for which CAC quantification was originally developed – modern CT scanners systematically underestimate CAC scores, which can be explained by overall higher noise levels in EBT due to limited photon flux.[41,42]

3.4. From quantification to characterization

The fourth shortcoming of the Agatston score is the *equal weighting* of calcifications in different coronary artery segments. The Agatston score is calculated regardless of the CAC location or distribution within the coronary artery tree (Fig. 3). However, distribution –such as proximal versus distal– of CAC may influence the prognostic value of CAC quantification.[43] Moreover, the Agatston score is based on the assumption that both higher volume and higher density of CAC are associated with increased cardiovascular risk. However, Criqui et al. showed that CAC density was inversely associated with cardiovascular risk.[44] Their study also showed that CAC volume was positively and independently associated with cardiovascular risk. Therefore, the prognostic value of CAC might be improved if scores accounted for differences in higher CAC volumes and lower CAC densities. Furthermore, current dual-energy CT and future photon-counting CT systems may allow for improved quantification of CAC densities due to material-decomposition imaging capabilities and high spatial resolution imaging for the latter technique.[45]

4. Alternative scoring methods

The limitations of the Agatston score have not gone unnoticed, and several alternative CAC quantification methods have been proposed, including calcium volume and mass scores.[16,17] Three-dimensional data allow the evaluation of the volume of calcifications in cubic millimeters. With appropriate calibration, facilitated by a calibration phantom CT table insert, the actual mass of CAC can be expressed in milligrams. For feasibility reasons, volume and mass scores are developed for the same CT acquisition settings as the Agatston score. Therefore, these methods are still affected by the same partial volume effects as the Agatston score itself. An advantage of both, volume and mass scoring methods is the linearity of CAC measurements, which in contrast to the ordinal Agatston score allows for more precise quantification. Another advantage is that both measures are not substantially affected by small variations in image noise. The volume score is the only score that is not weighted by density, which may be beneficial considering the equivocal association between CAC density and cardiovascular risk. Disadvantages of the mass score include the complicated acquisition method since a calibration phantom is needed for every exam. Also, CAC mass is underestimated on CT systems from all major vendors and results differ per vendor, worsening the inter-scanner reproducibility.[19,39,42] With these methods, calcifications with areas smaller than 1 mm^2 can be quantified in a more reproducible manner. Both volume and mass scores improve the reproducibility compared to Agatston scores.[6,33,35,46,47] However, to this date, these quantification methods are not used in a clinical and screening setting due to the lack of prognostic data and the need for phantom calibration.

5. Suggested solutions

An updated scoring method should entail a modification of CAC acquisition, reconstruction and quantification, which addresses the limits of reproducibility, spatial resolution, and allows taking advantage of modern radiation dose reduction techniques. First, the X-ray tube voltage should be reduced (e.g. to 100 kVp), which may not only result in lower radiation doses, but also increases the CT attenuation of less dense calcifications, allowing for improved detection and quantification of low-density CAC. Second, images should be reconstructed with thin slices (1 mm or less) resulting in isotropic images, allowing for precise three-dimensional CAC quantification, which may improve reproducibility. Reducing slice thickness and X-ray tube voltage will result in noisier images, particularly in larger patients; third, we recommend using noise reducing reconstruction methods, such as iterative reconstruction, to reduce image noise. Fourth, volumetric CAC scores should be quantified taking into account both volume and density (calibrated X-ray attenuation) of calcified plaque. Last, these higher quality datasets may allow refining risk estimates in the future by assessing the distribution of calcifications throughout the coronary tree, allowing for differentiation for example between diffuse and concentrated calcifications or proximal and distal calcifications. Machine learning algorithms may be helpful for these evaluations.

Since the Agatston score has already shown to be a strong and independent predictor of cardiovascular risk, an updated quantification method may not improve the predictive value substantially. Potentially, adding CAC distribution and shape may improve the predictive value. Also, using an inverse relation of CAC density and cardiovascular risk may be of incremental value. CAC distribution, shape, and inverse

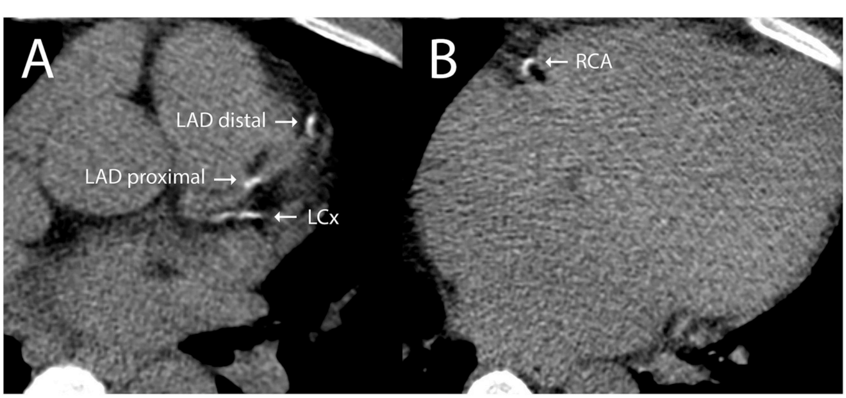

Fig. 3. Distribution of Calcifications. Calcium scoring CT scan of a 49-year old male with a total Agatston score of 265. The proximal and distal calcifications in the left anterior descending artery (LAD), as well as the calcifications proximally in the circumflex (LCx), and distally in the right coronary artery (RCA) contributed equally to the total risk score, whereas some of these calcifications may be prognostically more important.

density should be evaluated extensively in multiple cohorts before implementation in a new CAC scoring method. Replacing the Agatston score would require an update of current CAC reference values. This can potentially be done by retrospective recalculation of large CAC studies, such as the MESA database, or if not possible a new prospective study should be set up. Future research is thus indicated before the CAC quantification method can be improved. Independent of the added value of these features, the most important aim of a new score would be to allow for radiation dose reduction and improved reproducibility without compromised predictive value. Recently, evaluation of progression of CAC has gained interest.[48] Improving reproducibility of CAC quantification will inherently result in improved evaluation of CAC progression.

One should keep in mind that reductions in tube voltage and slice thickness and the application of iterative reconstruction will affect CAC attenuation and noise. Moreover, iterative reconstruction algorithms from different vendors result in different noise levels.[49] This may affect the ease CAC score of interpretation. Ideally, CAC attenuation and noise levels should be similar between CT systems from different vendors. This could be achieved by setting a single allowed slice thickness and a range of allowed noise levels and CAC attenuation using a standardized commercially available phantom. Another approach could be to determine conversion factors for every CT system by using a standardized commercially available phantom. This should be done for both small-sized patients and large patients since body size influences CAC attenuation and image noise.

6. Conclusion

The CAC quantification method has not been updated substantially since its introduction on EBT scanners in the early 1990s. In the meantime modern multiple-detector row CT systems have replaced EBT technology and current evidence indicates that the traditional Agatston score lacks in reproducibility resulting in subjects being incorrectly risk classified. Recent studies indicate that low-density CAC is associated with a higher cardiovascular risk and that the number, distribution and shape of CAC may be of prognostic value as well. The effects of these limitations on outcome prediction are not evaluated yet in large cohorts, however, we expect that more robust CAC quantification will enhance cardiovascular risk quantification. Therefore, we suggest optimizing CAC quantification for modern CT scanners using lower radiation doses and higher spatial resolution. Optimized images should be acquired at a low tube voltage allowing for detection of small and lower density calcifications and thin slices are reconstructed with iterative reconstruction allowing for more precise 3-dimensional CAC assessment to improve reproducibility. Lower tube voltage also decreases radiation exposure. Further research is needed to derive optimized CT acquisition and CAC quantification methods. Once optimized CAC quantification methods are developed, they should be evaluated in large observational studies with long follow-up time. We expect that optimized protocols will result in improved reproducibility and will allow for evaluation of CAC density, shape and distribution within the coronary artery tree at a reduced radiation dose.

In summary, the Agatston score has important limitations, including suboptimal reproducibility, spatial resolution and does not account for new image acquisition and reconstruction modes for current MDCT scanners. Therefore, we propose image acquisition, reconstruction and means to quantify coronary artery calcium should be optimized.

Disclosures

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