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Noninvasive quantification of coronary artery calcification: Methods and prognostic value

KEY POINTS

Evaluation of coronary artery calcium can allow early identification of coronary artery disease in patients with chronic renal failure.

Computed tomography (CT) is a noninvasive method for detecting coronary calcium.

Several scoring methods can be used to quantify CT-defined calcium load.

The additive value of calcium scoring in cardiovascular risk assessment remains controversial.

Caution is needed when extrapolating data on the prognostic value of coronary calcium quantification to patients with altered calcium metabolism, such as those with chronic renal failure.

PATIENTS WITH CHRONIC RENAL FAILURE are at increased risk for developing coronary artery disease (CAD).[1] Early identification of CAD in asymptomatic patients can reduce morbidity and mortality. One marker for CAD is coronary artery calcification. Studies in patients without chronic renal failure have shown that calcifications are present in atherosclerotic arteries and absent in normal vessels. Patients with chronic renal failure, however, have markedly altered clearance and metabolism of calcium, including extraosseous calcifications. The significance of the presence of calcium in the arteries of these patients is not yet well understood.

In view of heightened interest in coronary artery calcium in patients with chronic renal failure and end-stage renal disease, this article reviews noninvasive techniques for detecting and quantifying coronary calcium and the clinical significance of measured values.

RADIOLOGIC DETECTION METHODS

X-ray techniques such as computed tomography (CT) provide a noninvasive method for detecting coronary calcification. Because of its relatively high atomic number, calcium strongly attenuates x-rays. As a result, calcium appears bright on the CT image and is easily distinguishable from surrounding soft tissue without the need to administer an iodinated contrast agent, which could compromise patients with renal failure.

Two distinct CT technologies are capable of detecting coronary artery calcium: electron-beam CT (EBCT) and mechanical CT.

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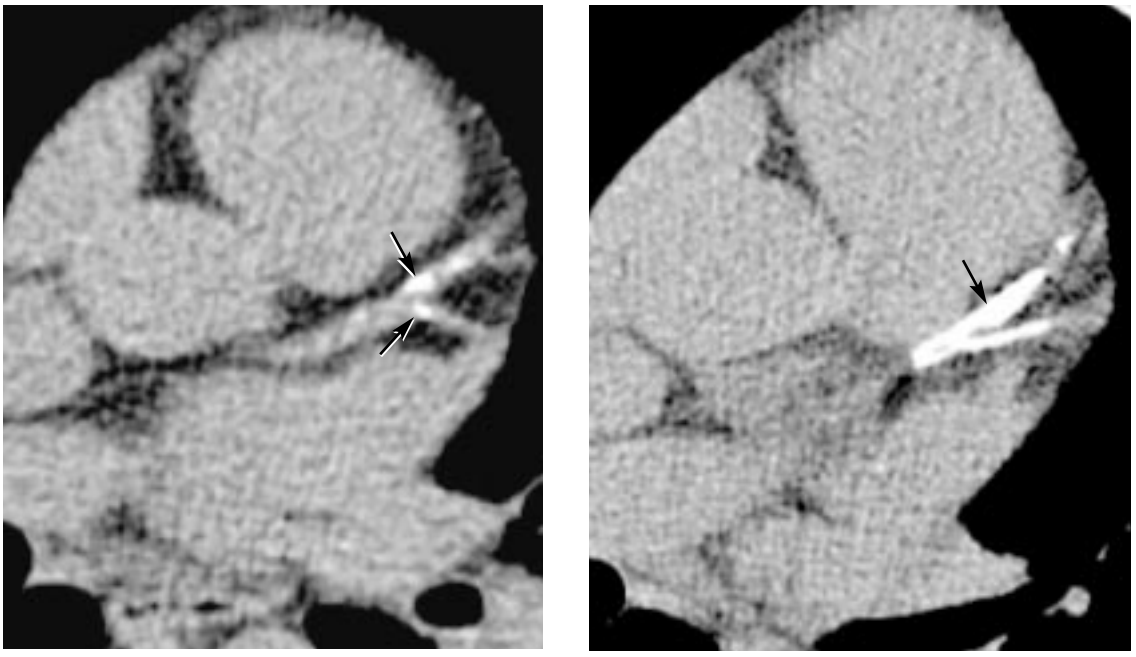

FIGURE 1. Mechanical multislice computed tomographic images of the left coronary system displaying mild (left) and severe (right) calcification (arrows).

Electron-beam CT

Most cardiac imaging with CT has been performed using EBCT, which is a well-established method for detecting coronary artery calcification.[2,3] With EBCT, x-rays are produced by decelerating electrons on a tungsten target ring encircling the patient.

Imaging is performed using either "step-volume" or "continuous-volume" scanning. Step-volume scanning refers to two-dimensional imaging in which a single transaxial slice is acquired and the patient table is moved to the next slice position. Continuous-volume scanning refers to three-dimensional imaging in which data are acquired during continuous rotation of the gantry and continuous movement of the patient table.

Step-volume scanning is the method most widely used for imaging of the coronary arteries because data acquisition can be referenced to the cardiac cycle using the patient's electrocardiographic (ECG) signal; data acquisition is triggered by the ECG signal during the diastolic phase of the cardiac cycle to minimize cardiac motion artifacts. Fast movement of the electron beam around the patient permits acquisition of a single axial image in 100 ms. For detection of coronary artery calcium, images are typically obtained with a thickness of 3 mm. The entire heart can be imaged during one or two breath-hold periods.

Mechanical CT

The establishment of mechanical CT for cardiac imaging has been more recent and followed the introduction of multislice CT (MSCT) scanners. State-of-the-art MSCT scanners capable of simultaneously acquiring four slices have facilitated the use of mechanical CT for detecting coronary artery calcification.

With mechanical CT, x-rays are produced in an x-ray tube rotating mechanically around the patient. Cardiac imaging is performed using either sequential scanning (analogous to step-volume scanning with EBCT) or spiral scanning (analogous to continuous-volume scanning). Both types of data acquisition can be referenced to the ECG signal. Slower movement of the mechanical system around the patient (compared with movement of the electron beam) requires at least 250 ms for acquisition of each image on currently available scanners.

For detection of coronary artery calcium, image thickness typically varies between 1.25 and 3 mm, depending on the method of MSCT data acquisition. With either the sequential or the spiral technique, the entire

Agatston scoring is the traditional method of quantifying coronary calcium

heart can be imaged during a single breathhold. **FIGURE 1** shows coronary artery images from patients with mild calcification and severe calcification obtained using sequential MSCT.

How the CT methods compare

Compared with EBCT, MSCT offers increased signal-to-noise ratios (because of the limited x-ray intensity of EBCT), shorter scan times, and higher spatial resolution. However, EBCT still has one major advantage—better temporal resolution and a resultant reduction of cardiac motion artifacts.

QUANTIFYING CORONARY CALCIUM

Calcium load in the coronary arteries can be quantified from either EBCT or MSCT images using different scoring algorithms. A recent study showed high correlation between EBCT and MSCT for calcium quantification.[4]

Agatston scoring

Any assessment of coronary calcification should also include a cardiovascular risk assessment

Agatston scoring, introduced in 1990, is the traditional method for quantifying coronary calcium with EBCT.[5] The method is based on the maximum x-ray attenuation coefficient, or CT number (measured in Hounsfield units [HU]), and the area of calcium deposits. First, calcified lesions are identified on CT images by applying a threshold of 130 HU to the entire image set; tissues with densities equal to or greater than the threshold are considered to correspond to calcium.

For each coronary artery, i, a region of interest (ROI) is drawn around each calcified lesion, j. The maximum CT number, CT_{ij}^{max}, of the ROI is determined and used to assign a weighting factor, w_{ij}. The area, A_{ij}, of the ROI is also determined. The Agatston score, S_{ij}, is computed as the product of the weighting factor and the area:

$$S_{ij} = w_{ij} \bullet A_{ij} \tag{1.1}$$

where

$$w_{ij} = \begin{cases} 1 \text{ if } 130 \text{ HU} \le CT_{ij}^{max} < 200 \text{ HU} \\ 2 \text{ if } 200 \text{ HU} \le CT_{ij}^{max} < 300 \text{ HU} \\ 3 \text{ if } 300 \text{ HU} \le CT_{ij}^{max} < 400 \text{ HU} \\ 4 \text{ if } 400 \text{ HU} \le CT_{ij}^{max} \end{cases} \tag{1.2}$$

The score for all lesions in all coronary arteries is summed to determine the total calcium burden:

$$S_{tot} = \sum_{i,j} S_{ij} \tag{1.3}$$

Although most existing data are based on Agatston scoring, this method has many limitations:

- It has a strong dependence on noise because it relies on the maximum CT number.
- Because weighting factors are used, the score increases nonlinearly with increases in the amount of calcium.
- Because the Agatston score was originally based on data from contiguous, nonoverlapping, 3-mm slices acquired with EBCT, the score as calculated using the above equations must be adjusted for non–3-mm slices and overlapping slices.
- The score does not correspond to a physical measure.

Volume scoring

Recent studies based on estimating the volume of calcium provide an alternative method of assigning a calcium score.[6–8] As with Agatston scoring, a threshold of 130 HU is applied and ROIs are drawn around each calcified lesion. For each ROI, the number of voxels exceeding the threshold is summed. The volume score is simply calculated as the product of the number of voxels containing calcium, N_{voxel}, and the volume of one voxel, V_{voxel}:

$$V_{ij} = V_{voxel} \bullet N_{voxel} \tag{1.4}$$

Again, the volume score of individual lesions is summed to obtain a total volume score:

$$V_{tot} = \sum_{i,j} V_{ij} \tag{1.5}$$

Volume scoring provides more reproducible results than Agatston scoring,[6,7] although it too has limitations. The volume score is vulnerable to overestimation of lesion size owing to partial volume effects; objects smaller than one voxel contribute to the score with the entire voxel volume. Also, the volume score does not necessarily represent the

true volume of calcium, which depends on the applied threshold. For this reason, the volume score is not a true physical measure.

Mass scoring

Quantification of calcium using absolute mass has also been proposed.[7,9] To obtain absolute values for calcium mass, a calibration measurement of a calcification with known hydroxyapatite density has to be performed and a calibration factor determined. The calibration factor, c_{HA}, is calculated as

$$c_{HA} = \frac{\rho_{HA}}{\overline{CT}_{HA} - \overline{CT}_{water}} \quad (1.6)$$

where ρ_{HA} is the density of the known calcification, $\overline{CT}_{HA}$ is the mean CT number of the known calcification, and $\overline{CT}_{water}$ is the mean CT number of water. Because the CT number of all materials except water depends on the x-ray spectrum, a specific calibration factor exists for each scanner and each scan protocol. The product of the calibration factor (c_{HA}), the volume (V_{ij}) as calculated in equation 1.4, and the mean CT number for each lesion ($\overline{CT}_{ij}$) gives the mass score (m_{ij}):

$$m_{ij} = c_{HA} \cdot V_{ij} \cdot \overline{CT}_{ij} \quad (1.7)$$

The total mass score is then the sum of the mass of all individual lesions:

$$m_{tot} = \sum_{i,j} m_{ij} \quad (1.8)$$

The mass score is given in milligrams and is a true physical measure. Initial results have shown mass scoring to be more reproducible than Agatston scoring,[7] but additional clinical studies must be performed.

HOW CALCIUM SCORING CONTRIBUTES TO RISK ASSESSMENT

The calcium–cardiac risk association

The prognostic value of quantifying coronary artery calcium has been reviewed extensively in several expert consensus documents.[2,3] Most information to date has been derived from Agatston scores obtained using EBCT. A significant association between coronary calcium scores and the risk for hard coronary events has been reported in studies in which the outcome evaluation was unadjusted for other cardiac risk factors.[10,11] A pooled analysis of the predictive value of EBCT Agatston scores from these studies showed an increase in positive predictive value and a corresponding decrease in negative predictive value with increasing calcium scores.[3]

Does calcium scoring have additive value?

On the other hand, additional studies that examined risk-adjusted outcomes that control for established cardiac risk factors failed to consistently show the incremental value of coronary calcium scores over traditional multivariate risk-assessment models such as the Framingham risk model.[12] The Framingham model is based on gender, age, blood pressure, cholesterol, high-density lipoprotein cholesterol, cigarette smoking, and plasma glucose. Detrano et al[13] reported that Agatston scores derived from EBCT added no significant incremental value to the risk determined from the Framingham and National Cholesterol Education Program risk factors. However, Taylor et al[14] concluded that the Framingham risk model and coronary calcium quantification were distinct methods of assessing risk for sudden cardiac death, and suggested a complementary role for these methods in identifying patients at high risk. Another study by Taylor et al[15] found that the Framingham risk model significantly underestimated the presence of premature, subclinical calcified coronary atherosclerosis in a cohort of low-risk subjects and recommended the use of calcium scoring as a screening test to identify persons needing to be promoted to a higher risk category.

The additive value of calcium scoring remains controversial, and any assessment of coronary calcification should also include a comprehensive cardiovascular risk-factor assessment.

Low or absent calcium scores have the greatest potential predictive value

Interpreting calcium scores

Guidelines have been proposed for interpreting Agatston scores for asymptomatic persons (**TABLE 1**).[16] They cover such issues as correlation to plaque burden, probability of significant CAD, implications for cardiovascular

TABLE 1

Recommended EBCT calcium score guidelines

EBCT CALCIUM SCORE	PLAQUE BURDEN	PROBABILITY OF SIGNIFICANT CAD	IMPLICATIONS FOR CV RISK	RECOMMENDATIONS
0	No identifiable plaque	Very low, generally < 5%	Very low	Reassure patient while discussing general public health guidelines for primary prevention of CV diseases
1–10	Minimal identifiable plaque burden	Very unlikely, < 10%	Low	Discuss general public health guidelines for primary prevention of CV diseases
11–100*	Definite, at least mild atherosclerotic plaque burden	Mild or minimal coronary stenoses likely	Moderate	Counsel about risk-factor modification, strict adherence with NCEP ATP II primary prevention cholesterol guidelines, daily ASA†
101–400*	Definite, at least moderate atherosclerotic plaque burden	Nonobstructive CAD highly likely, although obstructive disease possible	Moderately high	Institute risk-factor modification and secondary prevention NCEP ATP II guidelines. Consider exercise testing for further risk stratification
> 400*	Extensive atherosclerotic plaque burden	High likelihood (≥ 90%) of at least 1 "significant" coronary stenosis	High	Institute very aggressive risk-factor modification. Consider exercise or stress pharmacologic stress imaging to evaluate for inducible ischemia

*If score > 75th percentile for age/gender, advance to recommendations for next calcium score range.
†Oral administration of 80 to 325 mg.
ASA = acetylsalicylic acid; CAD = coronary artery disease; CV = cardiovascular; EBCT = electron-beam computed tomography; NCEP ATP II = National Cholesterol Education Program (Adult Treatment Panel II).

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risk, and recommendations for treatment. Guidelines for interpreting volume and mass scores have yet to be established.

Additional information for risk stratification can be gained from referencing a patient's calcium score to scores from asymptomatic individuals of the same gender and age to determine a percentile ranking. Reference databases exist for both Agatston scores and volume scores.[17] If a patient's Agatston score is greater than the 75th percentile for his or her age and gender, the patient is promoted to the next scoring range in TABLE 1.

Calcium scores have their greatest potential predictive value when they are absent or low (< 10 for Agatston scoring), which almost certainly indicates low risk for development of coronary heart disease.[2,3] Also, a positive calcium score may indicate that a patient considered to be at intermediate risk for coronary heart disease is actually at high risk—a finding that could particularly benefit asymptomatic patients in whom other risk factors could be modified.[2,3] Published evidence to date has not defined which asymptomatic patients would benefit from calcium scoring.

Calcium scoring in end-stage renal disease

It is not clear how much these observations apply to patients with chronic renal failure. Although the incidence of CAD is increased in patients with renal insufficiency, such patients also have altered calcium metabo-

lism.[1] Therefore, caution is needed when extrapolating available data to this special patient group. Further studies are needed to determine the additive predictive value of coronary calcium scoring for risk stratification in patients with renal failure.

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