Can total cardiac calcium predict the coronary calcium score?

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ABSTRACT

Background: Mitral annular calcification (MAC) shares the same risk factors as atherosclerosis and is associated with coronary artery disease as well as cardiovascular events. However, sensitivity and positive predictive value are low. We hypothesized that a global echocardiographic calcium score would better predict coronary atherosclerotic burden, as assessed by coronary artery calcium score (CAC), than MAC alone.

Methods: An echocardiographic score was devised to measure global cardiac calcification in a semi-quantitative manner; this included calcification in the aortic valve and root, the mitral valve and annulus, and the sub-mitral apparatus. This score, and a simplified version, were compared with a similar calcification score by CT scan, as well as the CAC.

Results: There was a good correlation between the two global calcification scores; the echocardiographic score also correlated with CAC. Using CAC >400 as a measure of severe coronary atherosclerosis, an echocardiographic score ≥5 had a positive predictive value of 60%. Importantly, the simplified score performed equally well (≥3 had a positive predictive value of 62%).

Conclusions: Global cardiac calcification, assessed by CT scan or echocardiography, correlates with the extent of coronary calcium. A semi-quantitative calcium score can be easily applied during routine echocardiographic interpretation and can alert the reader to the possibility of severe coronary atherosclerosis.

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Calcification of various cardiac structures is common as people age [1,2]. Mitral annular calcification (MAC) and aortic valve calcification share many clinical risk factors with atherosclerosis [3–5]. MAC is also associated with prevalent coronary artery disease and, to a lesser degree, clinical cardiovascular events [4–6]. It has been related to the extent and severity of coronary disease but sensitivity and positive predictive value are low [6,7].

Coronary calcifications are strongly correlated with coronary atherosclerosis and the coronary artery calcium (CAC) score obtained by CT scan can be used to make predictions about future coronary ischemic events [8–11]. CAC is reflective of the total burden of coronary atherosclerosis rather than stenosis severity [11,12]. Yet it adds independent prognostic value to the Framingham Risk Score for the prediction of coronary heart disease events with an absolute value >400 being associated with the highest risk.

Our hypothesis was that a global echocardiographic calcium score would better reflect the total coronary atherosclerotic burden, as assessed by CAC, than MAC alone. To test this hypothesis we devised a semi-quantitative echocardiographic calcium score and compared it with CT generated scores of coronary calcium and non-coronary cardiac calcium.

1. Methods

1.1. Determination of CAC score by CT scan

Patients who had clinically indicated cardiac CT scans performed from December 2005 to March 2008 were included. Most of these patients had equivocal stress tests and thus were at intermediate risk for coronary disease. Echocardiography databases were searched to identify those patients who also had an echocardiogram within 12 months of the CT scan. CT scans that were difficult to interpret due to excessive artifact (e.g. those with pacemaker leads, sternal wires, prosthetic valves, etc.) were excluded from the study. A study group of 41 subjects was produced. A 64 slice helical CT scanner (GE Light Speed VCT) was used. An initial scout scan performed prior to contrast administration was used for calcium scoring. All scans started just above the carina and extended to just below the diaphragm and included the entire coronary tree. Scans were done with breath held in inspiration, prospectively gated, with a field of view of 25 cm and slice thickness of 2.5 mm. The studies were done with 120 kV and the tube voltage ranged from 100 to 400 mA depending on body habitus.

The Agatston scoring method was used with a cutoff value above 130 Hounsfield units (HU) used to define calcification [13]. Lesion area was multiplied by a density factor derived from the maximal HU. The density factor was 1 for lesions with a maximum density of 130–199 HU; 2 for a maximum density of 200 to 299 HU; 3 for a maximum density of 300–399 HU and 4 for lesions with density ≥400 HU.

All images were reviewed on a work station (GE Advantage). A region of interest was drawn over the areas of calcification and the Agatston score was automatically
calculated by the software. Separate scores were calculated for the aortic root, aortic valve, mitral annulus, mitral valve, sub-mitral apparatus, and for the coronary arteries. For the calculation of aortic root calcium, only calcifications extending up to 2 cm above the sinus of Valsalva were used since this is the level that is most often imaged by standard transthoracic echocardiography. Any calcification that was seen as a ring, or part of a ring, at the aortic annulus was included as part of the aortic root and not as coronary or aortic valve calcium. All non-contrast CT scans used to assess CAC were compared with contrast enhanced CT scans as well. Contrast enhanced scans were reconstructed in multiple views using multiple windows so that circumflex coronary artery calcification could be delineated from mitral annular calcification. For instance, if circumflex coronary artery calcification was present in axial views of the contrast enhanced CT scans contrast could be seen in its lumen in almost all patients thus distinguishing it from MAC. Also curved planar reformatting of the arteries in the contrast CT scans was done and calcification following the path of the circumflex coronary artery was included as circumflex calcification and not MAC.

1.2. Determination of cardiac calcium by echocardiography

Echocardiograms were reviewed by two expert readers blinded to all clinical information as well as the CT scan results. A new echocardiographic calcium score was used as a semi-quantitative guide to overall calcification of the heart (Fig. 1). Similar to the CT scoring, this score also focused on the aortic valve and root, mitral valve and annulus, and sub-mitral apparatus. It was designed to account for the amount of calcification in each of these areas in a semi-quantitative fashion. Calcification was considered to be present when echo brightness exceeding that of normal valve tissue was seen. Pericardial echoes were often very bright and were not included in the score. Conversely, it was often not possible to discriminate between valvular sclerosis and calcification; both were included in the scoring.

The final echocardiographic calcium score was compared to various CT calcium scores. A simplified echo score (Fig. 2) was also compared with the CT scores. This simplified version scores a point each for the presence of calcium, regardless of amount, in the aortic valve, mitral valve/annulus and subarvalvular apparatus. An additional point is added if either valve is restricted in its opening. Figures 3 and 4 show examples of focal calcification in the aortic valve, mitral valve and subvalvular apparatus. MAC ≥5.0 mm in any dimension has been used to define severe MAC in previous papers [10,11]. It was also tested for its predictive value versus CT measures.

2. Statistical analyses

Continuous variables are presented as mean ± standard deviation and number and percentages for categorical variables. CAC score was not normally distributed (bimodal distribution), therefore we conducted our analyses using non-parametric tests. Furthermore, due to the non-linear relationship between the variables analyzed we used Spearman’s correlation coefficient (rho) between coronary calcium scores measured by CT and echocardiography. To identify the best cutoff for the echocardiographic calcium score to detect a coronary calcium score of ≥400 measured by CT, we constructed receiver operating characteristic curves and calculated their sensitivity, specificity and predictive values. Finally, we assessed the intra- and inter-observer variability for the echocardiographic calcium score by performing Spearman correlation between the two different measurements. Two-tailed p-values <0.05 were considered significant in advance. Intra- and inter-observer variabilities were assessed using Pearson’s correlation. Statistical analyses were performed using a statistical software package (JMP, version 7.0; SAS Institute; Cary, NC).

3. Results

The mean age of the subjects was 56 ± 13 years. Sixty-one percent (25/41) were women. The mean CAC in the sample was 947 (±2586). The mean echocardiographic calcium score was 3.4 (±2.5).

There was a positive correlation between age and the various CT measures (rho = 0.49/0.65/0.63 for non-coronary/coronary/total calcium). There was also a positive correlation between age and the echocardiographic scores (rho = 0.47/0.44 for total score/simplified score).

3.1. Reproducibility of the echocardiographic score

Intra-observer variability was assessed in 20 patients two weeks apart and there was an excellent correlation between the two readings (r = 0.87, p < 0.0001). Inter-observer variability was assessed in 20 patients by two blinded investigators (GSP and VMF) and showed excellent correlation (r = 0.80, p < 0.0001).

3.2. Evaluation of the total echocardiographic score

Comparing the total echocardiographic calcium score with the CT non-coronary calcium score yielded a positive and significant correlation (rho = 0.56, p < 0.0001). Comparing the total echocardiographic calcium score with the coronary calcium score also showed a significant positive correlation (rho = 0.46, p = 0.0026). By comparison, the CT non-coronary calcium score showed a somewhat better (positive) correlation with coronary calcium (rho = 0.63, p < 0.0001). Of note, there were 2 patients with coronary calcium scores >400 who had no other cardiac calcification detected either echocardiographically or by CT.

After performing ROC curves, an echocardiographic calcium score ≥5 had a sensitivity and specificity of 43% and 85% for detection of a CAC ≥400, with an area under the curve of 0.761. Positive and negative predictive values were 60% and 74%. When using a CAC ≥100 sensitivity and specificity were 35% and 86% with an area under the curve of 0.747. Positive and negative predictive values were 70% and 58%.

**Simplified Echocardiographic Score**

- AV calcification (0,1)
- MV or annular calcification (0,1)
- Subvalvular apparatus calcification (0,1)
- Restriction of either valve (0,1)

Fig. 2. AV = aortic valve; MV = mitral valve.

**Main Echocardiographic Score**

- Posterior Annulus (by thirds, score 0-3)
- PML restriction (0,1)
- Anterior annulus (0,1)
- AML restriction (0,1 [valve opening on LAX <= 10 mm])
- MV calcification (0,1 [mild], 2 [mild])
- Subvalvular apparatus calcification (0,1)
- AV calcification (0,1 [nodeles in < 3 leaflets], 2 [nodes in 3 leaflets but nonrestrictive], 3 [restrictive])
- Aortic root calcification (0,1)

Fig. 1. PML = posterior mitral leaflet; AML = anterior mitral leaflet; LAX = long axis view; MV = mitral valve; AV = aortic valve.
3.3. Evaluation of the simplified echocardiographic score

Comparing the simplified echocardiographic calcium score with the CT non-coronary calcium score yielded a positive and significant correlation (rho = 0.53, p = 0.0004). Comparing the simplified echocardiographic calcium score with the coronary calcium score also showed a significant positive correlation (rho = 0.44, p = 0.0041). When comparing the total and simplified echocardiographic scores, an excellent correlation was seen (rho = 0.91, p < 0.0001).

After performing ROC curves, a simplified echocardiographic calcium score ≥3 had a sensitivity and specificity of 57% and 81% for detection of a CAC >400. Positive and negative predictive values were 62% and 79%. When using a CAC >100 sensitivity and specificity were 50% and 86% with positive and negative predictive values of 77% and 64%.

3.4. Correlations using MAC alone

The prevalence of any MAC in this population was 54%; for MAC ≥5 mm it was 12%. Any MAC had a sensitivity and specificity of 71% and 56% for detecting CAC >400; positive and negative predictive values were 45% and 79%. When using a CAC >100 sensitivity and specificity were 65% and 57% with positive and negative predictive values of 59% and 63%.

MAC ≥5 mm in any dimension had a sensitivity of 29% and a specificity of 96% for detecting a CAC >400. Positive predictive value for CAC >400 was 80% and negative predictive value was 72%. When using a CAC >100 sensitivity and specificity were 20% and 95% with positive and negative predictive values of 80% and 56%. Of note, 1 patient with MAC ≥5 had CAC <100.

4. Discussion

Calcification of cardiac structures is common in the age groups typically treated by internists and cardiologists. MAC has been well studied and found to be associated with calcification of the aorta and the aortic valve [2,14]. When severe, MAC also predicts chronic kidney disease [15] and it can occasionally cause mitral stenosis [16]. It shares many risk factors with atherosclerosis [4,5]. Other types of extra-
coronary cardiovascular calcification (e.g. aortic valve and aorta) also share these risk factors [2]. In fact, MAC and aortic annular calcification have been shown to be highly associated with atherosclerotic disease in multiple vascular beds [17]. Similar observations lead Roberts to postulate that calcification of cardiac structures is a form of atherosclerosis [3].

MAC may thus be a visible barometer of atherosclerotic disease. However, it has been an inconsistent predictor of coronary disease [5]. This limitation may be due to lack of a good standard for its quantitative or semi-quantitative assessment. Or it may be that MAC alone correlates less well with coronary disease than the overall cardiac calcification. Cardiac structures often calcify in a nonuniform fashion [2]; one patient may have severe MAC with little aortic valve calcification while another may have the reverse and a third may have severe calcification of both. We therefore reasoned that a global echocardiographic score looking at the presence and severity of overall (non-coronary) cardiac calcification might better predict severe coronary disease than MAC alone.

4.1. The echocardiographic calcium score

The echocardiograms included in this study were all performed for clinical indications. Some were technically difficult but none were excluded on technical grounds. Compared to the CT non-coronary calcium score, the echo score showed a good overall correlation. There was a graded relationship noted at higher numbers of the echo score (>5). Still, there were instances of a high echo score and low CT non-coronary calcium score. These likely represent cases of valvular sclerosis or sclerosis. An echocardiographic calcium score ≥5 (or simplified score ≥3) was useful in predicting a high CT coronary calcium score. This is not the same as saying that a high echo score predicts severe coronary stenosis. However, coronary calcium closely tracks the total extent of atherosclerosis and a CAC score ≥400 has been shown in multiple studies to predict severe coronary atherosclerosis.

Quantitating calcium on echo is difficult. The amount of brightness detected is dependent on the quality of the study, gain settings used, and the care with which the study is performed. In addition we found it was not always possible to distinguish sclerosis from true calcification. For these reasons it was elected to use a semi-quantitative score and to include sclerotic lesions along with calcified lesions (also because sclerosis is a precursor of calcification or may contain focal calcification).

Finally, the echocardiographic score could not detect some patients with calcification of the aortic root as this area is not always well visualized. In addition, recent work shows descending aortic calcification to be more prevalent and more predictive of future events in angina patients versus ascending aortic calcification [21]. Transthoracic echocardiography cannot image most of the descending aorta though transesophageal echocardiography can.

4.2. Use of the echocardiographic scores for prediction of coronary artery calcium

Coronary calcium, as detected by CT scan, is highly correlated with the extent of coronary atherosclerosis (though not necessarily the severity of luminal stenosis) and predicts coronary ischemic events [10,18]. In particular, a CT coronary calcium score ≥400 has been associated with severe coronary disease, asymptomatic ischemia and cardiovascular events [10,11,19].

For the prediction of coronary calcium the echocardiographic calcium score showed a moderate correlation. This is consistent with previous studies [10,11]. However, an echo score ≥5 had a 60% positive predictive value for CAC ≥400. Thus, this level of cardiac calcification, when encountered on clinically indicated echocardiograms, should alert the physician to the possibility of severe coronary atherosclerosis. Interestingly, the simplified echo score at a cutoff of 3 had an equivalent positive predictive value (62%) to the full echocardiographic calcium score. This simplified score looks at the same areas of the heart originally noted by Roberts to commonly calcify [3]. It can be easily applied at the time of echo interpretation and serve as a marker of possible severe coronary atherosclerosis. It should be noted that this does not necessarily mean coronary stenosis. Rather it implies a heavy atherosclerotic burden and this does have prognostic import [12]. Because of positive remodeling, there can be extensive atherosclerosis without significant luminal narrowing [20].

By way of comparison, MAC ≥5 mm in any dimension was very specific for CAC ≥400 but was only found in 5 patients. The presence of any MAC had a low positive predictive value for severe coronary calcification.

5. Limitations

This was a retrospective study involving a small number of patients. All subjects were referred for cardiac CT on clinical grounds, a possible source of bias. Thus the findings cannot be considered definitive. The echocardiographic score should be tested in different populations and clinical situations. However, we were able to show the utility of the new echocardiographic score in assessing non-coronary cardiac calcification using CT scanning as a gold standard. An echocardiographic calcium score ≥5 (or simplified score ≥3) was used in predicting a high CT coronary calcium score. This is not the same as saying that a high echo score predicts severe coronary stenosis. However, coronary calcium closely tracks the total extent of atherosclerosis and a CAC score ≥400 has been shown in multiple studies to predict severe coronary atherosclerosis.

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