Measuring coronary artery calcification using positron emission tomography-computed tomography attenuation correction images

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Aims
Cardiac computed tomography (CT) measured coronary artery calcium (CAC-CT) is a well-validated and accurate tool for estimating atherosclerotic burden and prognosis. Computed tomography attenuation correction (ACCT) obtained during cardiac positron emission tomography (PET) has been used to visually estimate CAC; however, quantification using a non-gated ACCT images has not been described. We sought to understand the relationship between CAC measured using cardiac computed tomography (CT) and CAC using ACCT images obtained during cardiac PET perfusion imaging.

Methods and results
Patients with both CAC-CT and cardiac PET within 6 months of each other were identified. CAC-CT images were scored using the Agatston scoring method, while ACCT images were scored using different attenuation thresholds for calcium. CAC-CT and ACCT scores were compared. Between August 2007 and October 2010, 91 patients were included in the analysis. Interobserver reliability was excellent at all thresholds of detection tested. Pearson correlation was strongest between CAC-CT and ACCT at 50 HU threshold of detection (ACCT\textsubscript{50}). Implementing CAC categories (0, 1–100, 101–400, >400), there was a high degree of agreement between observers as well as between CAC-CT and ACCT\textsubscript{50}. Correlation was best for lower CAC scores; however, as CAC-CT increased, ACCT\textsubscript{50} underestimated CAC.

Conclusion
Quantifying CAC using ACCT images appears to be feasible and accurate. In a single cardiac PET examination, information regarding perfusion, LV function, flow quantification, and CAC can be obtained without additional radiation.

Keywords
Computed tomography • Coronary calcification • PET • Myocardial perfusion imaging • Attenuation correction

Introduction
Positron emission tomography (PET) myocardial perfusion imaging (MPI) is commonly used to diagnose haemodynamically significant coronary artery disease (CAD).\textsuperscript{1,2} However, this non-invasive modality lacks the ability to identify subclinical, non-obstructive CAD. Positron emission tomography/computed tomography scanners use low-dose, non-electrocardiogram (ECG) gated chest CT for attenuation correction (ACCT).\textsuperscript{3,4} There has been an interest in the additional clinical value of ACCT images and its potential use for the identification of patients with coronary artery calcification (CAC).

The assessment of CAC using CT (CAC-CT) is a well-validated method of identifying coronary atherosclerosis, estimating coronary atherosclerotic burden, and determining clinical prognosis.\textsuperscript{5} The visual estimation of CAC using ACCT images appears to agree with Agatston scores using conventional, non-contrast enhanced ECG-gated CT.\textsuperscript{6} However, the quantification of CAC using ACCT images has not been well studied.

The objective of this study is to understand the relationship between CAC measured using conventional cardiac CT images and ACCT images, and to identify a post-processing method that best estimates CAC using low-dose, non-ECG-gated ACCT images.
Methods
Between August 2007 to October 2010, 91 patients with both CAC scores and cardiac PET scans performed within 6 months of each other were identified. Patients with a prior history of CAD, coronary artery bypass grafting, or percutaneous coronary intervention were excluded. The local institutional review board approved this study.

Electrocardiogram gated CT calcium score
An ECG-gated cardiac CT was obtained as per local clinical routine. In brief, medications were administered targeting a heart rate ≤ 65 b.p.m. Using the GE-VCT scanner (General Electric Healthcare, Milwaukee, WI, USA), a non-contrast enhanced, prospective, ECG-gated image acquisition (400–800 mA, 120 kVp) was performed at the 70% phase and images were reconstructed with a 2.5 mm slice thickness and 25 cm field of view (FOV).

Computed tomography attenuation correction image acquisition
Using a 3D PET-CT 64-slice system (Discovery RX/VCT or 690/VCT, GE Healthcare, Milwaukee, WI, USA), a fast (2 s) low-dose (~0.4 mSv), helical (pitch: 0.984) non-ECG gated CT scan (140 kVp with axial and angular mA modulation, 20–210 mA range, at noise-index = 50) was acquired at normal mid-to-end expiration for attenuation correction. The radiation dose was calculated using a representative sample of 26 patients (DLP = 28 ± 12 mGy cm, conversion factor = 0.014 mSv/mGy cm). Standard CT images were reconstructed with a slice thickness of 3.75 mm and 70 cm FOV.

Coronary artery calcium measures
CAC-CT was separately scored using the GE Advantage Workstation (Smartscore Version 3.5, General Electric, Milwaukee, WI, USA) and Aquarius iNtuition software (Version 4.4.7, TeraRecon, Inc, San Mateo, CA, USA). CAC-CT was calculated using the Agatston scoring method. Mean values between the two workstations were included in the analysis of CAC-CT. ACCT images were scored for calcium by two independent readers using the Aquarius iNtuition software. The two readers were blinded to clinical information and all other CAC measures. ACCT scores were measured using varying thresholds for which calcium is detected. Acknowledging the lower sensitivity of ACCT, lower thresholds (50, 75, 100, and 130 HU) were selected ‘a priori’. All other Agatston thresholds, weighting factors, and area calculations remained unchanged. Careful anatomical surveillance was performed to exclude noise and calcified non-coronary structures (such as the aorta, mitral annulus, and aortic valve). When identifying CAC on ACCT images, regions of interest were manually placed on structures believed to be coronary calcification, rather than all structures above the predefined threshold. Large discrepancies in ACCT measures were resolved by consensus reading between the two observers. The mean values from the two readers were used in the analysis. Ten control ACCT cases (not included in the analysis) were used for the training and calibration of readers prior to analysing study patients. In addition, ACCT for CAC was visually estimated by two observers blinded to the CAC-CT results.

Statistical analysis
Statistical analyses were performed using SAS (version 9.2, SAS Institute Inc., Cary, NC, USA). Statistical significance was defined as P < 0.05. Continuous variables were expressed as means with standard deviations. Categorical variables were expressed as frequencies with percentages. The predictive capability of CAC using the ACCT images was evaluated using a linear regression model, while the stability of this prediction model was further validated using the bootstrap with 1000 replications.

As the best measure of reliability for continuous data, intraobserver and interobserver reliability for CAC measures were assessed using intraclass correlation (ICC) coefficients. Likewise, ICC was also used to evaluate the agreement between CT and ACCT measures of CAC using different thresholds of attenuation (ACCT50, ACCT75, ACCT100, ACCT130 HU) in addition to CAC visually estimated from ACCT (ACCTvisual). The intra-observer reliability for CAC measures was also evaluated graphically using a Bland–Altman plot which demonstrates both the overall degree of agreement and whether the agreement is related to the underlying value of the item. The agreement between categorical CAC-CT and ACCT (0, 1–100, 101–400, >400) was expressed as Kappa with a 95% confidence interval.

Results
A total of 91 patients (mean age 60.3 ± 11.1 years, 58.2% men) were included in the analysis (Table 1). The agreement between CAC-CT measures using the GE Advantage and TeraRecon Aquarius workstations was excellent [ICC0.999, (Table 2)]. Similarly, ACCT interobserver variability using the different thresholds was also excellent (Table 2). Interobserver variability proved to be best for the ACCT130 [ICC = 0.997 (95% CI: 0.996–0.998)], but still excellent at a threshold of 50 HU [ICC = 0.974 (95% CI: 0.961–0.983)]. ACCTvisual had the greatest interobserver variability [ICC = 0.903 (95% CI: 0.857–0.935)].

<table>
<thead>
<tr>
<th>Table 1 Baseline characteristics</th>
<th>Patients (n = 91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60.3 ± 11.1</td>
</tr>
<tr>
<td>Men (n = 53)</td>
<td>58.2%</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>30.8 ± 6.9</td>
</tr>
<tr>
<td>Pre-test likelihood for CAD (%)</td>
<td>30.1 ± 30.9</td>
</tr>
<tr>
<td>Mean time between CT scan and PET scan (days)</td>
<td>76.4 ± 50.5</td>
</tr>
<tr>
<td>Median time between CT scan and PET scan (days)</td>
<td>66</td>
</tr>
<tr>
<td>Cardiac risk factors</td>
<td></td>
</tr>
<tr>
<td>Smoking/ex-smoking</td>
<td>55 (60.4%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>55 (60.4%)</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>59 (64.8%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>11 (12.1%)</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>34 (37.4%)</td>
</tr>
<tr>
<td>Indications for study</td>
<td></td>
</tr>
<tr>
<td>Chest pain</td>
<td>52 (57.1%)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>19 (20.9%)</td>
</tr>
<tr>
<td>Other</td>
<td>20 (22.0%)</td>
</tr>
<tr>
<td>CT imaging parameters</td>
<td></td>
</tr>
<tr>
<td>Imaging heart rate</td>
<td>55.8 ± 6.4</td>
</tr>
<tr>
<td>Radiation (mSv)</td>
<td>2.42 ± 0.66</td>
</tr>
</tbody>
</table>

CAD, coronary artery disease.
Intraclass and Pearson correlation demonstrated a very strong relationship between CAC-CT and ACCT scores (Table 3, Figure 1) with the best correlation observed between CAC-CT and ACCT50 \( \text{ICC} = 0.953 \) (95% CI: 0.930–0.969), \( r = 0.954 \).

Using standard CAC categories (Agatston score = 0, 1–10, 11–100, 101–400, 401–1000, >1000), interobserver ACCT50 agreement was excellent \( \text{kappa} = 0.899 \) (95% CI: 0.828–0.970) with 92.3% of reads scored within the same category and the remainder within one category of each other. Similarly, when clinically applicable CAC categories utilizing a four-level scale (0, 1–100, 101–400, >400) were used, \( \text{kappa} = 0.941 \) (95% CI: 0.884–0.998). When CAC-CT and ACCT130 scores were compared, the degree of agreement was poor \( \text{kappa} = 0.329 \) (95% CI: 0.192–0.465). Similarly, the agreement between CAC-CT and ACCTvisual was modest \( \text{kappa} = 0.561 \) (95% CI: 0.432–0.690). To determine systematic bias, a Bland–Altman plot was constructed (Figure 2). Correlation appeared best for lower CAC scores and as CAC-CT increased, ACCT50 appeared to underestimate CAC. The receiver operator characteristic (ROC) curve showed a high degree of accuracy for ACCT50 in the prediction of the presence of CAC \( \text{AUC} = 0.963, P < 0.0001 \) (Figure 3). Forty-one patients (66%) with normal PET MPI and normal myocardial blood flow were found to have CAC.

### Table 2 Interobserver variability

<table>
<thead>
<tr>
<th></th>
<th>ICC (95% CI)</th>
<th>Bland Altman plot ( \bar{X} ) ± 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAC-CT</td>
<td>0.999 (0.999–0.999)</td>
<td>(-7 \pm 24.4)</td>
</tr>
<tr>
<td>ACCT130</td>
<td>0.997 (0.996–0.998)</td>
<td>119.8 ± 298.6</td>
</tr>
<tr>
<td>ACCT100</td>
<td>0.993 (0.989–0.995)</td>
<td>83.2 ± 224.7</td>
</tr>
<tr>
<td>ACCT75</td>
<td>0.982 (0.973–0.988)</td>
<td>52.5 ± 197.4</td>
</tr>
<tr>
<td>ACCT50</td>
<td>0.974 (0.961–0.983)</td>
<td>17.1 ± 171.7</td>
</tr>
<tr>
<td>ACCTvisual</td>
<td>0.903 (0.857–0.935)</td>
<td>(-31.1 \pm 260.8)</td>
</tr>
</tbody>
</table>

CAC-CT, cardiac computed tomography coronary artery calcium; ACCT, computed tomography attenuation correction (subscript denotes the threshold of detection for coronary artery calcium); ICC, intraclass correlation; HU, hounsfield units.

*Bland Altman Plot calculated as \( [(\text{CAC-CT}) - (\text{ACCT})]/\text{mean (CAC-CT)} + (\text{ACCT})\).
Discussion

The current study is the first to quantify CAC using ACCT images obtained during PET MPI and shows that coronary artery calcium can be quantitatively measured. There was a high degree of correlation between the two methods for scoring CAC with the highest degree of correlation found for ACCT50. There was very good interobserver variability but underestimation by ACCT50 when CAC exceeded 400. The need for a reduced HU threshold for ACCT likely relates to the low tube potential (20–210 mA) used in ACCT scans resulting in poor image contrast and increased susceptibility to attenuation and noise. However, with lowering the HU threshold for ACCT, there is a greater reliance upon the skill of the observer to differentiate between CAC and artefact or non-coronary calcification.

Although interobserver variability for scoring CAC using ACCT scans was excellent at all thresholds of detection, interobserver variability (ICC) was best with higher HU thresholds. High HU thresholds decrease susceptibility to noise and increase specificity of CAC detection, which also results in higher reproducibility. However, high HU thresholds would underestimate total CAC by missing lower attenuating calcific plaque, hence reducing CAC-CT and ACCT agreement and thus systematically underestimating CAC. Conversely, lower thresholds improve the detection of calcium and its estimation but at the expense of greater interobserver variability. Hence, it was determined that the combination of interobserver variability and agreement of CAC-CT and ACCT appeared to be best using ACCT50, which also appeared to yield the best combination of accuracy in predicting CAC. In our study, ACCTvisual (visual estimation of CAC) had greater interobserver variability and inferior agreement with CAC-CT than ACCT50 measures. In the ROC analysis, detection of CAC using ACCT50 was robust with an AUC of 0.963. Using the clinical calcium scoring classification (0, 1–100, 101–400, >400), there was excellent agreement between CAC-CT and ACCT50 with most calcium scores falling within the same category (79%) and the remainder within one category.11–15 This suggests that the ACCT50 measure of CAC may provide prognostic information and improve patient risk stratification especially in cases with normal myocardial perfusion. However, the incremental prognostic value of ACCT50 requires further investigation.

An important strength of nuclear perfusion imaging is in its ability to determine patient prognosis and future adverse cardiac events.16 Recent data have confirmed the incremental prognostic value of cardiac PET to predict future adverse cardiac events based upon perfusion scan results.17–19 However, despite its significant advantages, cardiac PET may under-diagnose subclinical, non-flow limiting coronary artery atherosclerosis.2 Prior studies have shown that PET-derived myocardial blood flow (MBF) quantification may be decreased in patients with non-obstructive CAD or CAC.20,21 Although this may be true in patients with severe atherosclerotic burden, the impact of mild atherosclerosis is uncertain. In our study, 66% of patients (41/62) with normal PET MPI and MBF were found to have CAC, suggesting that some patients with coronary atherosclerosis may have preserved MBF.

Computed tomography data used for attenuation correction in SPECT or PET MPI improves diagnostic accuracy and confidence in interpretation by reducing or entirely eliminating attenuation artefacts.4,22 Quantification of coronary artery calcium has been shown to have independent and incremental prognostic value for survival.23,24 Additionally, calcium scoring has incremental additive prognostic value when applied to the Framingham risk factors.23 Bybee et al.25 showed that in 760 patients referred for cardiac PET perfusion imaging, 64.1% has evidence of subclinical CAD defined as the presence of calcium on a separate CAC scan. Hence, it may be desirable to combine an objective quantifiable measure of CAC with PET MPI. A recent study showed that CAC using standard CT could also be used for PET attenuation correction.26 Although possible, this has not been routinely adopted into clinical practice and the increased radiation exposure associated with CAC-CT would need to be considered. Thus, before this can be implemented, one must establish whether calculation of CAC using ACCT is feasible and accurate.

A recent study by Einstein et al.6 showed that visual estimation of CAC from ACCT scans had excellent agreement with CAC-CT with good interobserver reliability. Additionally, prior studies using low-dose ungated CT scans for lung cancer screening compared
with standard protocol CAC-CT scan have shown good reliability in predicting the presence of CAC. However, CAC-CT scans and low-dose ungated CT scan (ACCT acquisition protocols) differ fundamentally. Whereas the CAC-CT scan is typically prospectively ECG gated to minimize radiation and cardiac motion artefact, the ACCT scan used in perfusion imaging is a non-gated, low-dose acquisition scan. ACCT scans typically utilize a lower tube current, a larger FOV, and thicker slices. Similarly, typical radiation doses for CAC scans range from 0.6 to 5.6 mSv depending on different vendors, whereas radiation doses for ACCT scans are roughly 0.3 mSv. Thus, rest/stress low-dose perfusion imaging with Rb-82 3D PET and ACCT CAC could be provided with <2 mSv total dose.

Given these differences, the greatest concern with ACCT scans is the under-diagnosis of CAC due to the inability to detect very small calcific plaque. In our study, 17% of patients were classified as having no calcium on ACCT but had calcium on CAC-CT. This was similar to the results of Einstein et al. who report an incidence of 22%. More importantly, a large proportion of patients (66%) with normal PET MPI had CAC, thus highlighting that patients with normal myocardial perfusion may still have subclinical coronary atherosclerosis. Blaha et al. showed that patients with CAC scores between 1 and 10 had at least a two-fold increase in events over patients without calcium. We acknowledge that ACCT had a false negative rate of 17% which may be undesirable. However, the incremental prognostic benefit of CAC detection over PET MPI is uncertain and additional studies are needed. We believe that the potential benefit may be in those patients with normal PET MPI, but with coronary calcification, thus identifying those patients that may benefit from more aggressive risk stratification. Further, large prospective trials are required to elucidate the benefit of CAC scoring above PET MPI and the effects of statin therapy on CAC.

Limitations
Due to the potential for cardiac motion artefact in non-ECG-gated acquisition scans, significant blurring of calcium can result in which a region of calcium may seem larger than it otherwise is. This can appear as a calcific plaque with a dense centre surrounded by a less dense periphery as a result of the actual segment of calcium moving spatially during the acquisition phase. Each observer manually selected the region of calcium according to which they believed encompassed a true calcific plaque. However, delineation could be difficult and the region had to be manually placed and potentially subject to reader expertise. In addition with each decrease in threshold for detection of calcium (100, 75, 50 HU), the automated calcium detection software would routinely select non-calcified regions of increased density. Individual observers again attempted selection of the dense structures interpreted as coronary artery calcium, while identifying and excluding non-coronary calcium and dense extra-coronary structures (Figure 4).

In our study, CAC was calculated according to the method described by Agatston et al. Another method for calculating CAC is the volume method which potentially may be used to calculate CAC from ACCT. The volume method utilizes the isotropic interpolation technique to calculate the volume of a lesion.
above 130 HU. An advantage of this method includes the ability to account for over or undersampling for different slice parameters. Likewise, the volume method may have superior reproducibility over the Agatston score. However, the volume method may overestimate true plaque volume. Prior studies using low-dose un gated CT scans for lung cancer screening compared with standard protocol CAC-CT scan have shown excellent concordance (kappa = 0.89) between Agatston score ranks. Thus, given prior experience, validation, and the clinical acceptance of the Agatston score, a similar methodology was chosen for this study. Another potential limitation is the underestimation of CAC from partial volume averaging due to the fewer and thicker (3.75 vs. 2.5 mm) reconstructed slices. This may result in lower CAC scores thus necessitating a lower threshold for CAC detection. However, the underestimation of small areas of calcium may be acceptable acknowledging that low CAC scores have excellent prognostic and that the underestimation of small CAC may have little impact upon the total CAC score. Finally, as different vendors may have different ACCT acquisition protocols, our HU thresholds for quantifying CAC may not directly apply to other ACCT acquisition protocols (i.e. slow free-breathing ACCT scans). Rather, a modification of the presently described method could be used to quantify CAC.

Conclusion

The quantification of CAC using ACCT scans obtained during cardiac PET MPI is feasible and appears to correlate well with CAC. In a single-cardiac PET MPI examination, the clinician may be able to obtain information regarding perfusion, LV function, and flow quantification while simultaneously obtaining complimentary information regarding CAC without the need for additional radiation. Larger prospective studies to determine the incremental value of ACCT CAC over PET MPI are required.

Conflict of interest: B.J.W.C. receives research and fellowship support from GE Healthcare and educational support from TeraRecon Inc. R.S.B. is also a consultant for Lantheus Medical Imaging and Jubilant DRAXimage, and receives restricted grants from Lantheus Medical Imaging, GE Healthcare, MDS Nordion. R.A.d. is a consultant for DRAXimage, has unrestricted grant support from GE Healthcare and educational support from Jubilant DRAXimage, and receives restricted grants support from GE Healthcare and ACCTimage, and receives license revenues from DRAXimage and the University of Ottawa Heart Institute.

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References

Caseous calcification of the mitral valve complicated by embolization, mitral regurgitation, and pericardial constriction

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A 64-year-old man presented with amnesia and was found to have multiple cerebral lesions on magnetic resonance imaging (MRI) (Panel A). Thoracic computed tomography excluded malignancy, but found pericardial calcification (Panel B, red arrows) and mitral annular calcification (Panel B, white arrows). Transthoracic and transoesophageal echocardiography revealed sub-valvular apparatus calcification below the posterior mitral valve leaflet (PMVL) with mild mitral regurgitation (see Supplementary data online, Movies S1 and S2) and no other potential source of embolism.

Cardiovascular MRI showed a mass in the region of the PMVL communicating with the pericardial space (Panels C–H, white arrows; see Supplementary data online, Movie S3). The mass was hyperintense on T1 and T2 weighting with a hypointense nodule, suggesting a fluid-filled lesion and calcified core (Panel E, white arrow). The adjacent pericardium was calcified and significantly thickened (Panels E and F, red arrows). Early and late gadolinium-enhancement imaging demonstrated a hyperenhancing fibrous cap surrounding a non-enhancing (avascular) core (Panel G). Caseous calcification of the mitral valve with pericardial involvement was diagnosed. Six months later, the mass had regressed and much of the caseous material had disappeared (Panels D, F, and H, white arrows). Pericardial calcification remained unchanged (Panel F, red arrows), but there was now a septal bounce and clinical signs of pericardial constriction (see Supplementary data online, Movies S4 and S5). Significant mitral regurgitation due to PMVL tethering was now seen on cine imaging (Panel D, yellow arrow; see Supplementary data online, Movie S6).

Caseous calcification is usually benign, but valvular dysfunction and embolization of necrotic material have been described. In addition, this case reports extensive pericardial involvement—most likely a result of necrotic material rupturing into the pericardial space.

Supplementary data are available at European Heart Journal - Cardiovascular Imaging online.

Conflict of interest: none declared.

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