Registry for the Evaluation of the PROgnostic value of a novel integrated imaging approach combining Single Photon Emission Computed Tomography with coronary calcification imaging (REPROSPECT)

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Aims

Although an added diagnostic and prognostic value of the global coronary artery calcification (CAC) score as an adjunct to single-photon emission computed tomography (SPECT)-myocardial perfusion image (MPI) has been repeatedly documented, none of the previous studies took advantage of the anatomic information provided by the unenhanced cardiac CT. Therefore, no co-registration has so far been used to match a myocardial perfusion defect with calcifications in the subtending coronary artery. To evaluate the prognostic value of integrating SPECT-MPI with CAC images were obtained from non-enhanced cardiac computed tomography (CT) for attenuation correction to predict major adverse cardiac events (MACE).

Methods and results

Follow-up was obtained in 462 patients undergoing a 1-day stress/rest 99mTc-tetrofosmin SPECT and non-enhanced cardiac CT for attenuation correction. Survival free of MACE was determined using the Kaplan–Meier method. After integrating MPI and CT findings, patients were divided into three groups (i) MPI defect matched by calcification (CAC ≥1) in the subtending coronary artery (ii) unmatched MPI and CT finding (iii) normal finding by MPI and CT. At a mean follow-up of 34.5 ± 13 months, a MACE was observed in 80 patients (33 death, 6 non-fatal myocardial infarction, 9 hospitalizations due to unstable angina, and 32 revascularizations). Survival analysis revealed the most unfavourable outcome (P < 0.001 log-rank test) for patients with a matched finding.

Conclusion

In the present study, a novel approach using a combined integration of cardiac SPECT–CAC imaging allows for refined risk stratification, as a matched defect emerged as an independent predictor of MACE.

Keywords

Cardiac hybrid imaging • Coronary Calcium score • SPECT–CT • Prognostic value of SPECT–CAC

Introduction

Coronary calcification is one of the key components of the atherosclerotic plaque in patients with coronary artery disease (CAD). Several studies have demonstrated the feasibility and incremental prognostic value of the coronary artery calcium (CAC) score beyond and above traditional cardiovascular risk factors,1,2 suggesting that the CAC score is a useful clinical marker to predict...

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cardiovascular risk in patients with CAD. Despite technical advances which have enabled multimodality imaging, the clinical value of integrating CAC and single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) has not been investigated yet. Fusion of both imaging modalities would allow to anatomically match calcifications of distinct coronary vessels with the perfusion abnormality in a given myocardial territory served by this artery similar to the recently introduced hybrid imaging with MPI and coronary computed tomography angiography (CCTA),5 while avoiding the use of contrast medium. For MPI–CCTA hybrid imaging,6 the diagnostic7–9 and prognostic value10,11 as well as its favourable impact on treatment strategy12 and downstream resource utilization13 has been extensively documented recently.

Notably, a matched finding of a coronary stenosis associated with a perfusion abnormality in the respective territory as assessed by SPECT-MPI has been shown to be a strong predictor of an adverse outcome.10 Whether a match of a perfusion defect in a myocardial territory with a calcification of its subtending coronary artery confers a similar prognostic predictive value is unknown. As this technique is easier to perform, involves a lower radiation dose, may be more cost-effective, and avoids the use of contrast medium, it may represent an attractive alternative to true hybrid imaging. Thus, the aim of the present study was to evaluate whether integration of coronary calcifications with perfusion information, which can be visualized by a hybrid image offering a panoramic view of the heart, allows identification of patients at an increased risk for an adverse cardiac event.

We hypothesized a superiority of such SPECT–CAC hybrid imaging in cardiovascular stratification over SPECT only.

**Methods**

**Patient population**

We enrolled 509 consecutive patients who were referred for the evaluation of known or suspected CAD by SPECT-MPI with attenuation correction by low-dose unenhanced cardiac computed tomography (CT). Patients were followed up for the occurrence of major adverse cardiac events (MACE), which included: all-cause death, non-fatal myocardial infarction, unstable angina requiring hospitalization, and coronary revascularization. The first event in each patient was used for the survival analysis. To avoid a confounder between diagnostic accuracy and prognostic prediction of SPECT–CAC, all patients with revascularization within the first 30 days were excluded from the present study.

The need for written informed consent was waived by the institutional review board (local ethics committee) due to the nature of the study with sole clinical data collection. The study population was partly shared with the cardiac imaging registry reported elsewhere.10

**Single-photon emission computed tomography myocardial perfusion imaging**

Patients underwent a 1-day electrocardiography (ECG)-gated stress/rest protocol. Pharmacological stress was induced by infusion of adenosine at a standard rate (0.14 mg/min/kg) over 6 min followed by a dose of 300–350 MBq 99mTc-tetrofosmin injected 3 min into the pharmacological stress. After a delay of 45–60 min, ECG-gated stress images were acquired. Thereafter, a three-fold higher dose of 99mTc-tetrofosmin was administered followed again by a delay of 45–60 min before acquisition of the ECG-gated rest data. An unenhanced low-dose CT scan for X-ray-based attenuation correction was additionally performed which can be utilized for coronary calcium assessment as previously reported.13,14 The SPECT-MPI acquisition was obtained on a dual-head camera (Millenium VG and Hawkeye or Ventri, both GE Healthcare, Milwaukee, WI, USA). For image analysis, a commercially available software package (Cedars QGS/QPS; Cedars-Sinai Medical Center, Los Angeles, CA, USA)15 was used. Perfusion defects were identified as previously reported.16

**Coronary artery calcium score**

A low-dose, unenhanced CT for SPECT-MPI attenuation correction was performed on a LightSpeed VCT XT stand-alone scanner (GE Healthcare) using the following scanning parameters: prospective ECG triggering, 2.5-mm slice thickness, 120 kV tube voltage, 200 mAs per rotation tube current, and a large scan field of view of 50 x 50 cm.13 From this scan, Agatston scores for each coronary vessel were computed with commercially available software (SmartScore 4.0, GE Healthcare) and summed to yield the total CAC, as previously reported.17 A total CAC > 300 was considered as a high risk according to Detrano et al.1

**Data interpretation**

The SPECT and CAC images were analysed independently by two experienced nuclear cardiologists. In the case of disagreement a consensus between both was reached. A matched finding was defined as a SPECT-MPI defect at stress in a territory supplied by a calcified coronary artery (CAC score > 0 in this artery). All other combinations of pathological findings were classified as unmatched. Thus, in order to assess the prognostic value of hybrid imaging, all patients were assigned to one of the following three categories:

(i) matched: SPECT-MPI defect and calcification in the subtending coronary artery (as defined above);

(ii) unmatched: any unmatched pathological finding from SPECT-MPI and/or unenhanced coronary CT;

(iii) normal: no pathological finding, i.e. no coronary calcification by low-dose unenhanced CT and no defect by SPECT-MPI.

To illustrate a matched and an unmatched finding, two hybrid images were reconstructed by image fusion of SPECT with low-dose CT performed on a dedicated workstation (Advantage Workstation 4.3, GE Healthcare) using the CardIQ Fusion software package (GE Healthcare) as previously described in detail5 and presented in Figure 1.

**Statistical analysis**

For statistical testing, SPSS software (SPSS 19.0, SPSS, Inc.) was applied. Quantitative variables were expressed as mean ± standard deviation and categorical variables as frequencies or percentages. Survival analysis was performed by the Kaplan–Meier method. The log-rank test was used to compare the survival curves. Univariate and multivariate Cox proportional hazard regression models were used to identify independent predictors of cardiac events. Variables were selected in a stepwise forward selection manner; entry and retention sets with a P < 0.05 were considered to indicate a significant difference. Variables included in the models were age, male gender, presence of three or more cardiac risk factors (hypertension, hypercholesterolaemia, smoking, diabetes mellitus, a positive family history for CAD), abnormal MPI, and coronary calcification. A risk of variable was expressed as a hazard ratio with corresponding 95% confidence interval. P-values < 0.05 were considered as a statistically significant difference.
Results

Study population
We enrolled 509 consecutive patients who underwent non-invasive imaging for the evaluation of known or suspected CAD by SPECT with CT-based attenuation correction. Of these patients, 47 (9.2%) were excluded due to missing follow-up or CT artefacts from implanted devices (stents, pacemakers) precluding meaningful CAC evaluation \( n = 20 \) or early revascularization \( n = 27 \). The remaining 462 patients were included in the final analysis as they successfully underwent both SPECT-MPI and unenhanced coronary CT for attenuation correction from which coronary calcifications were assessed and a CAC score was calculated. The mean age of the study population was 63.4 ± 11.3 years and 316 (68.4%) patients were male. Patient characteristics are given in Table 1.

SPECT-MPI and coronary calcium CT findings
SPECT-MPI revealed normal perfusion in 350 (75.8%) patients and an abnormal perfusion finding in 112 (24.2%) patients. Forty-five patients (9.7%) had a reversible defect, 44 (9.5%) patients had a fixed defect, and 23 (5.0%) a partially reversible defect.

A normal CT examination (i.e. no coronary calcifications) was observed in 94 (20.3%) patients, whereas coronary calcifications were found in 368 (79.7%) patients.

A matched pathological hybrid finding (MPI defect with corresponding coronary vessel calcification) was observed in 100 (21.6%) patients. Unmatched findings were present in 274 (59.3%) patients. Eighty-eight (19.0%) patients revealed no coronary calcification and no MPI defect and were therefore classified as normal.

Follow-up data
During 34.5 ± 13 month of follow-up, a MACE was observed in 80 patients (17.3%), including death in 33, non-fatal myocardial infarction in 6, hospitalization due to unstable angina in 9, and revascularization in 32 patients.

We observed 36 (36%) MACE in the matched group \( n = 100 \) and 44 (16%) in the unmatched group \( n = 274 \), while no MACE occurred in the normal group \( n = 88 \).

According to Kaplan–Meier survival curves the matched group had the most unfavourable outcome (log-rank test \( P < 0.001 \) for MACE and \( P < 0.01 \) for death and MI) (Figure 2). On both univariate and multivariate analysis, the presence of \( \geq 3 \) risk factors and a matched hybrid finding emerged as independent predictors of MACE (Table 2).

Six patients with CAC = 0 were reclassified from low risk to intermediate risk (unmatched finding) by the presence of a perfusion abnormality. Furthermore, 35 patients with CAC 1 to 300

### Table 1: Baseline characteristics stratified to normal, unmatched, and matched findings (in study population \( n = 462 \))

<table>
<thead>
<tr>
<th></th>
<th>Normal ( n = 88 )</th>
<th>Unmatched ( n = 274 )</th>
<th>Matched ( n = 100 )</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>53.8 ± 11.7</td>
<td>64.7 ± 10.5</td>
<td>68.5 ± 9.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>38 (43.2)</td>
<td>171 (62.4)</td>
<td>69 (69.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obesity (%)</td>
<td>25 (28.4)</td>
<td>58 (21.2)</td>
<td>24 (24.0)</td>
<td>0.365</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>10 (11.4)</td>
<td>42 (15.3)</td>
<td>26 (26.0)</td>
<td>0.015</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>21 (23.9)</td>
<td>70 (25.2)</td>
<td>71 (71.0)</td>
<td>0.139</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>47 (53.4)</td>
<td>168 (61.3)</td>
<td>29 (29.0)</td>
<td>0.040</td>
</tr>
<tr>
<td>Family history (%)</td>
<td>20 (22.7)</td>
<td>83 (30.3)</td>
<td>29.0 (29.0)</td>
<td>0.390</td>
</tr>
<tr>
<td>Hypercholesterolaemia (%)</td>
<td>27 (30.7)</td>
<td>106 (38.7)</td>
<td>51 (51.0)</td>
<td>0.014</td>
</tr>
<tr>
<td>&gt; 3 risk factors (%)</td>
<td>26 (29.5)</td>
<td>83 (30.0)</td>
<td>44 (44.0)</td>
<td>0.030</td>
</tr>
</tbody>
</table>
were reclassified from an intermediate risk (Detrano et al.4) to high risk by a matched finding. Finally, 115 patients with CAC > 300, but no matching perfusion abnormality, were reclassified from a high risk (Detrano et al.4) to an intermediate risk due to the unmatched hybrid finding. Thus, a total of 156 (33.3%) patients were reclassified by our method. With regard to the unmatched findings, there were 262 patients with MPI+/calcium−, and six patients with MPI+/calcium+ (in unmatched territories).

Discussion

In this study, we show for the first time that fused images integrating MPI with the presence of coronary calcification in CCTA allowed for improved risk stratification in patients with known or suspected CAD. In fact, a matched perfusion calcification finding on a hybrid image was a strong predictor of MACE.

So far, hybrid imaging has been established by combining MPI with CCTA. The matching of perfusion findings with the exact
coronary anatomy as obtained from the contrast-enhanced CCTA has resulted in a substantial added diagnostic and prognostic value as documented in the past years.\textsuperscript{5,7,9,18} However, the application of contrast material and substantial additional radiation dose from CCTA has limited a widespread use in clinical routine. In contrast, the SPECT–CAC hybrid approach does not require any contrast material application and a native CT for attenuation correction and CAC is routinely performed at a radiation dose lower than that required for CCTA scanning. In fact, although an impressive reduction in the radiation dose for CCTA to values as low as 1–2 mSv has been achieved with modern protocols,\textsuperscript{19,20} many centres have not yet implemented these novel protocols resulting in a high radiation dose exposure of the patients examined.\textsuperscript{21}

CAC scanning is a modern non-invasive tool that was initially introduced to screen for atherosclerosis in asymptomatic subjects. Over the last decade, however, its use has been expanded to the assessment of the extent of calcifications and prognosis in patients with suspected CAD. While coronary CCTA provides greater accuracy for the diagnosis of CAD, global CAC reflects the total atherosclerotic burden. It has been reported that the global calcium score added incremental prognostic information over myocardial perfusion indicating a stepwise increase in cardiac events with an increased global calcium score irrespective of myocardial perfusion.\textsuperscript{22} However, our results suggest that the presence of calcifications in a coronary artery serving a myocardial territory with a perfusion defect as illustrated by a hybrid approach might identify patients at an even further increased risk for an adverse outcome than the global calcium score alone. Therefore, combining quantitative information on an anatomic burden of CAD in terms of coronary calcification with functionality of its territory might have further consequences for risk stratification.

The novelty of the present study is the concept of integrating findings of coronary calcification including the information of its specific topographic anatomic location within the vascular tree with MPI for the assessment of prognosis. This can be presented as a hybrid image, which illustrates whether a perfusion defect is in the target territory subtended by a calcified coronary artery representing a matched finding. This information conferred a high added value as it led to reclassification of one-third of our study population.

Hybrid images integrating anatomic information from CCTA and functional information from MPI by image fusion has been shown to improve the diagnostic and prognostic evaluation of CAD.\textsuperscript{5,10,19,23} The main strength of this technique\textsuperscript{24,25} is the correct assignment of a coronary artery to its subtended territory, which is much superior to mental integration due to the large individual variability of the coronary tree.

The present study is the first to document the prognostic value of such matched findings of cardiac SPECT–CAC imaging without using any contrast material, as patients with a coronary calcification and a matched perfusion defect in MPI are at highest risk for future cardiac events.

The advantage of such performance is that firstly, unenhanced CT is widely accessible due to the growing availability of SPECT–CT devices, secondly, CT attenuation correction confers an added diagnostic as well as a prognostic value in SPECT-MPI,\textsuperscript{23,26} and thirdly the protocol for CAC from attenuation correction is validated.\textsuperscript{13,14} Besides the low radiation dose exposure from non-enhanced CT the lack of necessity for contrast material is another major advantage, particularly in elder patients with clinically unknown renal impairment or those with potential iodine allergy who should not undergo CT investigation with contrast material. Results from studies comparing CCTA with MPI suggest that a large proportion of patients with suspected CAD but normal perfusion has evidence of subclinical atherosclerosis as revealed by CAC.\textsuperscript{13,27–29} In classic MPI–CT hybrid imaging, the MPI findings complement the CT anatomic information by allowing an instant assessment of the functional significance of such stenosis.\textsuperscript{6,30,31} The CAC reflects the anatomic burden of coronary calcification but the way it is generally used, i.e. just assessing a total score of the entire coronary tree does not help localize disease to identify its topographic association with functional myocardial ischaemia.

Several studies have addressed the added diagnostic and prognostic value of CAC combined with MPI due to the relative ease to obtain global CAC. The present study is the first to take advantage of the anatomic imaging of coronary calcification and the ability to match these findings with the anatomically corresponding myocardial territory by an integration of CAC and MPI. From the large CAC study of Budoff et al.,\textsuperscript{2} it is well known that the

**Table 2** Predictor of events on Cox proportional hazards regression models (in study population n = 462)

<table>
<thead>
<tr>
<th>MACE (n = 80)</th>
<th>Univariate HR (95% CI)</th>
<th>P-value</th>
<th>Multivariate HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.02 (0.99–1.04)</td>
<td>0.235</td>
<td>NA</td>
<td>NS</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.80 (0.50–1.25)</td>
<td>0.329</td>
<td>NA</td>
<td>NS</td>
</tr>
<tr>
<td>≥3 risk factors</td>
<td>2.12 (1.35–3.32)</td>
<td>0.001</td>
<td>2.08 (1.34–3.24)</td>
<td>0.001</td>
</tr>
<tr>
<td>MPI</td>
<td>1.15 (0.60–2.19)</td>
<td>0.670</td>
<td>NA</td>
<td>NS</td>
</tr>
<tr>
<td>CAC &gt;0</td>
<td>1.99 (0.90–1.90)</td>
<td>0.918</td>
<td>NA</td>
<td>NS</td>
</tr>
<tr>
<td>Matched MPI/calcification*</td>
<td>2.15 (1.25–3.86)</td>
<td>0.005</td>
<td>3.20 (2.06–5.00)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CAC, coronary artery calcium score; HR, hazard ratio; MPI, myocardial perfusion imaging.

*Vessel-based calcification.
involvement of an artery with regard to having calcification or not is a predictor of events as strong as the absolute amount of CAC in each artery.

**Study limitations**

It could be perceived as a limitation to our study that we have used all-cause mortality which is not a direct cardiac endpoint. We have chosen this endpoint as it represents the most solid endpoint, since it is easy to be adjudicated without a potential for bias. Secondly, abnormal MPI failed on multivariate analysis as an independent predictor of MACE, which is in contrast to some previous studies. This is at least in part attributable to the fact that the present analysis included integrated MPI–CAC findings on top of MPI findings, which are linked by interaction. Furthermore, we did not differentiate between small vs. pronounced extent and severity of MPI defects, which would have most probably resulted in a cut-off above which prognostication would be successful. In addition, 27 patients were excluded from analysis due to early revascularization prompted by large ischaemic findings, which therefore fell out of the final analysis. However, the lack of the prognostic impact of MPI in our study strengthens our results, as a matched SPECT–CAC finding nevertheless emerged as an independent predictor.

Similarly, we did not evaluate the correlation between the extent of coronary calcification and outcome as this is well established. However, the fact that a matched finding irrespective of the extent of an MPI defect, and the CAC score is a strong predictor of MACE, strengthens the validity of our data and the simplicity of its applicability in daily routine.

Thirdly, data from MPI on the one hand and for attenuation correction and CAC imaging on the other hand were acquired on separate stand-alone scanners, and hybrid images were obtained by software fusion. Thus, misalignments could result in mismatch. However, the fusion software has been previously validated. Finally, our data do not allow a final conclusion on whether the present study results can be extrapolated to settings with less high-end CT devices (either stand-alone or hybrid scanners with 16- or less slices).

**Conclusions**

This is the first study showing that combining cardiac SPECT–CAC imaging allows risk stratification, as a matched defect emerged as an independent predictor of MACE.

**Acknowledgments**

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**Conflict of interest:** none declared.

**References**


