Automated calcium scores collected during myocardial perfusion imaging improve identification of obstructive coronary artery disease

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Abstract

Background: Myocardial perfusion imaging (MPI) is an accurate noninvasive test for patients with suspected obstructive coronary artery disease (CAD) and coronary artery calcium (CAC) score is known to be a powerful predictor of cardiovascular events. Collection of CAC scores simultaneously with MPI is unexplored.

Aim: We aimed to investigate whether automatically derived CAC scores during myocardial perfusion imaging would further improve the diagnostic accuracy of MPI to detect obstructive CAD.

Methods: We analyzed 150 consecutive patients without a history of coronary revascularization with suspected obstructive CAD who were referred for 82Rb PET/CT and available coronary angiographic data. Myocardial perfusion was evaluated both semi quantitatively as well as quantitatively according to the European guidelines. CAC scores were automatically derived from the low-dose attenuation correction CT scans using previously developed software based on deep learning. Obstructive CAD was defined as stenosis >70\% (or >50\% in the left main coronary artery) and/or fractional flow reserve (FFR) <0.80.

Results: In total 58\% of patients had obstructive CAD of which seventy-four percent were male. Addition of CAC scores to MPI and clinical predictors significantly improved the diagnostic accuracy of MPI to detect obstructive CAD. The area under the curve (AUC) increased from 0.87 to 0.91 (p: 0.025). Sensitivity and specificity analysis showed an incremental decrease in false negative tests with our MPI + CAC approach (n = 14 to n = 4), as a consequence an increase in false positive tests was seen (n = 11 to n = 28).

Conclusion: CAC scores collected simultaneously with MPI improve the detection of obstructive coronary artery disease in patients without a history of coronary revascularization.

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1. Introduction

Angina pectoris (AP) is a clinical syndrome characterized by episodes of retrosternal complaints, usually induced by exercise or other stress factors with quick relieve after discontinuation of exercise or stress. AP is often caused by myocardial ischemia due to the presence of obstructive coronary artery disease (CAD) and/or microvascular dysfunction [1,2]. The diagnostic assessment of patients with suspected obstructive CAD is challenging and one of the most common aspects of cardiology nowadays. Since the presence of obstructive CAD often requires coronary intervention, accurate diagnostic tests are of great importance.

Myocardial perfusion imaging (MPI) with positron emission tomography (PET)/computed tomography (CT) is an accurate non-invasive test for patients with suspected obstructive CAD [3,4]. It provides measurements on myocardial perfusion, myocardial blood flow (MBF) and coronary flow reserve (CFR). The coronary artery calcium (CAC) score on the other hand is a powerful predictor for cardiovascular events [5–9]. Recent studies have demonstrated additional diagnostic power of the CAC score on top of perfusion imaging in patients with suspected obstructive CAD [10–13]. For these studies an additional ECG triggered CT-scan was acquired for manual assessment of CAC scores instead of using the attenuation correction CT images gathered during MPI. Several studies compared manual CAC scoring on an ECG triggered CT with manual CAC scoring on attenuation correction CT images and showed encouraging results [14–16]. Recently, two studies performed in our center compared manual CAC scoring on ECG triggered CT images with automated CAC scoring in low dose chest CT and attenuation correction CT [17,18]. Both studies used a previously developed algorithm based on deep learning and showed that this is a reliable and accurate method of calculating the CAC score.

Therefore, the aim of our study is to assess whether automatically derived CAC scores simultaneously collected with MPI on attenuation correction CT images improve the diagnostic accuracy of MPI in patients with suspected obstructive CAD.

2. Materials and methods

2.1. Study population

The MYOMARKER (MYOcardial ischaemia detection by circulating biomARKers) study is a prospective single-center observational cohort study of consecutively enrolled patients (>18 years of age) with suspected CAD who presented at the outpatient clinic of the Meander Medical Center (Amersfoort, the Netherlands) between August 2014 and September 2016. All patients underwent a Rubidium-82 PET/CT scan as part of their diagnostic work-up.

The complete cohort consists of 1265 patients. For the purpose of this study only patients who underwent coronary angiography (CAG) within 90 days prior to or after MPI were selected. After exclusion of patients with previous coronary artery bypass grafting (CABG) or previous percutaneous coronary intervention (PCI), and exclusion of five patients with incomplete MPI results, the final cohort consisted of 150 patients (Appendix A, Fig. A1). The study was approved by the regional medical ethics committee and performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

2.2. PET-CT imaging

A detailed description of MPI imaging protocol is provided in the supplemental materials (Appendix B). Briefly, patients were asked to discontinue caffeine- or methylxanthine-containing food/drinks and theophylline and dipyridamol 48 h prior to the PET/CT scan. Rubidium-82 PET/CT scans were acquired using a hybrid scanner (Biograph CT Flow 64-slice scanner, Siemens Healthcare, Knoxville, Tennessee). Rest and stress cardiac PET/CT images were acquired on the same day, pharmacological stress was administered intravenously with regadenoson. The estimated effective radiation dose for this protocol to the patients was 3.7 mSv. Heart rate, systolic blood pressure and 12 lead ECG were recorded at baseline, 1 min after regadenoson administration and after imaging. Rate-pressure product was calculated for manual correction of rest flow values.

2.3. PET image analysis

Myocardial perfusion was evaluated according to the European guideline in two ways: semi-quantitative and quantitative [19]. All scans were evaluated by 2 experienced observers. Semi-quantitative analysis was performed with the use of the 17-segment model of the American Heart Association [20], in short; the summed difference score (SDS) is the difference between the perfusion deficit score in stress and rest, a SDS score > 4 was defined as stress induced ischemia. Quantitative analysis of myocardial perfusion was assessed by the myocardial blood flow (MBF, mL/g/min) and coronary flow reserve (CFR). CFR was computed from the dynamic rest and stress imaging series with commercially available software (Siemens Syngo Dynamic PET). A global MBF was calculated for the left ventricle as well as regional MBF for each of the three coronary vessel territories. Resting MBF was manually adjusted for the patient-specific rate-pressure product at rest. Global and regional coronary flow reserve was defined as the ratio of hyperemic to (adjusted) baseline MBF.

MPI scans were considered as normal if a patient had a normal MBF, CFR and a SDS score of 0. Normal MBF refers to normal MBF at a threshold of 2.0 mL/g/min. Normal CFR was set 1.6. MPI Scans were considered as suspect for obstructive CAD if either an SDS score Stress > 4 was measured, or patients with an SDS between one and three but with abnormal MBF and/or wall motion abnormalities (WMA).

2.4. Calcium scoring

CAC scores were determined from the low-dose attenuation correction CT scan, which were derived during MPI using a previously developed algorithm [17]. This software was originally developed for fully automated calcium scoring in low dose chest CT scans. We therefore manually annotated coronary calcium calculations in 200 consecutive CT scans from the present study and retrained the software with a combination of low dose chest CT and low dose attenuation correction CT scans. Briefly the software first detects the lungs to identify a region of interest in the image and then automatically detects CAC above the standard threshold of 130 Houndsfield Units using a deep learning approach. Detected calcifications are labeled according to the affected coronary vessel (left anterior descending including left main coronary artery, left circumflex artery and right coronary artery. CAC scores were calculated for all three coronary vessels [21]. Since this new method is not able to distinguish previously placed coronary stents from coronary calcium we excluded patients with coronary stents from the analysis. CAC scores were categorized according to previous literature as 0, 1–100, 101–300 and 301 or more [5,22].

2.5. Coronary angiography

All lesions were measured by quantitative coronary angiography (QCA) by a blinded trained clinical physician (MD), using Cardiovascular Angiography Analysis System software (CAAS 7.3, Piezon Medical Technologies, Knoxville, TN). Lesions were defined as stenoses of 50% or more. The percentage of diameter stenosis was measured at the narrowest point of the lesion.
Medical Imaging, Maastricht, The Netherlands). In case of uncertainty a board certified interventional cardiologist (GL) was asked to measure the lesion as a second observer. Uncertainty was mostly based on doubts regarding the second frame in which the lesions should be measured. Lesions were considered hemodynamically important if: 1. FFR positive ≤0.80 or 2. A luminal stenosis >70% (or >50% in case of left main) measured with QCA. In case of discrepancy between FFR measurement and QCA measurement, FFR result was considered more reliable and therefore used. In total, 15 lesions were measured with FFR.

2.6. Statistical analysis

Continuous data are expressed as mean ± standard deviation (SD), categorical data as frequencies and percentages. Differences in continuous variables were compared by independent t-test. Dichotomous variables were compared by Fisher's exact test. Univariable logistic regression was performed for all variables that were considered possible clinical predictors based on previous literature or differences in baseline characteristics. All variables with a P value <0.20 in the univariable analysis were used for the multivariable analysis. Statistical tests were two-sided with a critical significance level of <0.05. Statistical analysis were performed with SPSS version 25.0 (SPSS, Chicago, IL) and R software (R software, version 3.4.1).

3. Results

3.1. Clinical patient characteristics

Clinical characteristics are shown in Table 1. The mean age was 68 ± 12 years, and the majority of patients was male (64%). Patients

| Demographics | All N = 150 | No obstructive CAD N = 63 | Obstructive CAD N = 87 | P value* |
|--------------|------------|---------------------------|------------------------|----------|
| Age in years | 67.6 (11.5) | 66 (10.39) | 68 (12.23) | 0.470 |
| Male sex     | 96 (64%)   | 29 (48%) | 67 (74%) | 0.001 |
| BMI          | 28.1 (5.4) | 28.7 (6.3) | 26.9 (4.6) | 0.291 |

| Medical history | All N = 150 | No obstructive CAD N = 63 | Obstructive CAD N = 87 | P value* |
|-----------------|------------|---------------------------|------------------------|----------|
| History of CVD  | 111 (74%)  | 41 (68%) | 70 (78%) | 0.196 |
| History of CAD  | 25 (17%)   | 3 (5%) | 22 (24%) | 0.002 |
| History of MI   | 18 (12%)   | 2 (3%) | 16 (18%) | 0.008 |
| History of PAD  | 10 (7%)    | 3 (5%) | 7 (8%) | 0.504 |
| Diabetes mellitus | 35 (23%) | 14 (23%) | 21 (23%) | 0.575 |
| Hypertension    | 97 (65%)   | 36 (60%) | 61 (68%) | 0.329 |
| Dyslipidemia    | 87 (58%)   | 37 (62%) | 50 (56%) | 0.458 |
| Current smoker  | 39 (26%)   | 15 (25%) | 24 (27%) | 0.820 |
| BMI             | 28.1 (5.4) | 28.7 (6.3) | 26.9 (4.6) | 0.783 |

| Medication | All N = 150 | No obstructive CAD N = 63 | Obstructive CAD N = 87 | P value* |
|------------|------------|---------------------------|------------------------|----------|
| Platelet aggregation inhibitors | 85 (57%) | 29 (48%) | 56 (62%) | 0.093 |
| Anticoagulants | 30 (20%) | 11 (18%) | 19 (21%) | 0.667 |
| Beta-blockers | 81 (54%) | 31 (52%) | 50 (56%) | 0.640 |
| Statins | 87 (58%) | 37 (62%) | 50 (56%) | 0.458 |
| ACE inhibitor or ARB | 57 (38%) | 19 (32%) | 38 (42%) | 0.192 |
| Calcium channel blockers | 34 (23%) | 16 (27%) | 18 (20%) | 0.339 |
| Looopdiuretics | 22 (15%) | 9 (15%) | 13 (14%) | 0.925 |
| Nitroglycerin | 57 (38%) | 22 (37%) | 35 (39%) | 0.784 |

Table 1

Clinical characteristics of all patients with and without obstructive CAD.

| 13Reb PET-CT findings | All N = 150 | No obstructive CAD N = 63 | Obstructive CAD N = 87 | P value* |
|------------------------|------------|---------------------------|------------------------|----------|
| Rest LVEF              | 58 (16)   | 61 (17) | 57 (16) | 0.670 |
| Stress LVEF            | 61 (17)   | 61 (17) | 69 (16) | 0.947 |
| SDS                    | 4 (5)     | 1 (2) | 6 (4) | <0.001 |
| RFP                    | 11,024 (3068) | 10,341 (2258) | 11,501 (3458) | 0.227 |
| Rest MBF uncorrected   | 1.15 (0.38) | 1.12 (0.33) | 1.17 (0.42) | 0.511 |
| Rest MBF corrected     | 0.86 (0.25) | 0.89 (0.24) | 0.83 (0.25) | 0.170 |
| Stress MBF             | 2.41 (1.88) | 2.61 (0.77) | 2.28 (2.35) | 0.313 |
| CFR                    | 3.19 (0.99) | 3 (1) | 3 (1) | 0.584 |

CAC results

| All N = 150 | No obstructive CAD N = 63 | Obstructive CAD N = 87 | P value* |
|-------------|---------------------------|------------------------|----------|
| 0           | 8 (5%) | 5 (8%) | 3 (3%) | 0.038 |
| 1–100       | 27 (18%) | 17 (27%) | 10 (12%) | 0.007 |
| 101–300     | 26 (17%) | 14 (22%) | 12 (14%) | 0.043 |
| >300        | 89 (59%) | 27 (43%) | 62 (71%) | <0.001 |

Continuous variables are presented as mean (SD), categorical variables as n(%). * P value for comparison between groups with and without obstructive CAD. CVD = cardiovascular disease, CAD = coronary artery disease, MI = myocardial infarction, PAD = peripheral artery disease. Aspirin, clopidogrel or ticagrelor, LVEF = Left ventricular ejection fraction. SDS = Summed Difference Score [15], RFP = rate pressure product, MBF = myocardial bloodflow, CFR = Coronary flow reserve, CAC = Coronary Artery Calcium.
patients with obstructive CAD was higher compared to those with stress and rest in all patients. As expected, the average SDS score in all patients. The left ventricular ejection fraction was above normal limit during infarction (18% vs. 3%, p value 0.008). There were no differences in age, BMI, or any of the other known risk factors for cardiovascular disease between patients with and without obstructive CAD. These variables were used for multivariable analysis, finally after model reduction with the likelihood ratio test male sex and history of CAD remained significant predictors of obstructive CAD.

3.3. Diagnostic performance of combined models

Table 2 provides an overview of the estimated diagnostic parameters in clinical practice for three single parameters

| Measure | TP | TN | FP | FN | Sensitivity | Specificity | PPV | NPV | AUC (95%CI) |
|---------|----|----|----|----|-------------|-------------|-----|-----|-------------|
| Ischemia* | 76 | 49 | 11 | 14 | 0.84 | 0.82 | 0.87 | 0.78 | 0.83 (0.76–0.90) |
| CAC score | 67 | 38 | 22 | 23 | 0.74 | 0.63 | 0.75 | 0.62 | 0.69 (0.60–0.78) |
| Ischemia_CAC score† | 86 | 32 | 28 | 4 | 0.96 | 0.53 | 0.75 | 0.89 | 0.74 (0.66–0.83) |

Table 2 shows the final three constructed models. The first model contains the clinical predictors (male sex and history of CAD) for the presence of obstructive CAD selected with multivariable logistic regression. In the second model the presence of ischemia on MPI (SDS ≥ 4, or SDS 1–3 and abnormal MBF/WMA) was added to the first model. CFR was considered as possible MPI-derived predictor for the presence of obstructive CAD, but it showed no additive effect on the model performance (OR 1.10 95% CI 0.78–1.58 p value 0.501 appendix C1). In the third model, CAC score was added on top of the second model. Both the presence of ischemia on MPI (OR 26.49, 95%CI 9.45–74.24) and the CAC score (OR 2.47, 95% CI 1.40–4.34) were significant predictors for the presence of obstructive CAD in addition to the clinical predictors. Corresponding ROC curves with AUC values are shown in Fig. 1. The diagnostic accuracy of MPI to detect obstructive CAD improved with 4% when adding the automatically derived CAC scores (0.87 vs. 0.91). This difference in AUC between model 2 and 3 was statistically significant, p value 0.025.
comparing the use of the presence of ischemia alone, CAC scores (dichotomized as either <300 or >300) alone and presence of ischemia and/or a CAC scores above 300. When comparing MPI result on its own (AUC 0.83, 95% CI 0.76–0.90) with only CAC scores (AUC 0.69, 95% CI 0.60–0.78), both sensitivity (0.84 vs. 0.74) and specificity (0.82 vs. 0.63) were better in the model with only MPI, according to existing literature. Addition of CAC scores to MPI data substantially reduced the number of false negative tests (from n = 14 to n = 4 patients), which leads to a remarkable increase of the sensitivity and positive predictive value. As a consequence, the number of false positive tests is increased (from n = 11 to n = 28), which affects the specificity and positive predictive value of the tests.

4. Discussion

This study was a proof-of-concept to see whether our algorithm could automatically determine CAC scores on low-dose CT images gathered during MPI. We showed that presence of ischemia and CAC scores were both significant predictors of obstructive CAD in addition to clinical parameters. We have shown that addition of these CAC scores increased the diagnostic accuracy of MPI to detect obstructive CAD (AUC increase 4%, p value for difference 0.025). The increased diagnostic yield is mainly due to the reduction of false negative test results (N = 14 to N = 4). Important counterpart to this finding was the increased number of false positive tests (N = 11 to N = 28), this needs further research.

4.1. Predictors of obstructive coronary artery disease

In line with previous studies, history of CAD, ischemia and the CAC score were significant predictors for the presence of obstructive CAD [3,5,7,9]. In contrast, none of the generally accepted risk factors (smoking, diabetes, hypertension and dyslipidemia) for obstructive CAD were significant predictors in our population [2]. This might be the result of our high risk study population, namely only patients referred for CAG were included. The same is seen in previous comparable studies [12,13].

In our results CFR did not contribute to the prediction of the presence of obstructive CAD (OR 1.10 95%CI 0.78–1.58). Several studies established an association between low CFR and adverse cardiovascular outcomes [23–26]. However, they did not use CFR as a predictor of obstructive CAD. Taqueti et al. showed that impaired CFR is not only a marker of epicardial disease but especially a marker of diffuse nonobstructive CAD and microvascular dysfunction [27]. They state that CFR might be especially useful in women and diabetic patients. The limited added diagnostic value of CFR in our study was therefore not surprising.

4.2. Diagnostic performance of MPI and automated CAC score

Diagnostic performance of MPI and automated CAC score alone were in agreement with previous literature [2]. Existing literature on the added value of CAC scoring in addition to MPI is limited. Bybee et al. analyzed patients with a negative MPI and found subclinical atherosclerosis in 22–30% of the patients with the use of CAC scores [28]. Thompson et al. showed 17% reclassification of patients with normal MPI results into having obstructive CAD after adding CAC scores [29]. Schepis et al. observed the added value of CAC scores in patients with suspected obstructive CAD [11]. They showed an increased sensitivity of MPI after adding CAC scores from 76% to 83%. In our study an even larger beneficial effect was observed (increase of 84% to 96%). Zampella et al. showed an AUC of a combined model with CAC score and MPI (without clinical parameters) of 0.79 [13]. Regardless of our much more heterogeneous population we showed similar results (AUC combined model 0.74, 95% CI 0.66–0.83). Danad et al. showed that the incremental value of a combined assessment of PET with coronary CT also depends on which nuclear tracer is used [30]. An important difference between existing literature and our study is the use of a fully automated CAC scoring algorithm, which makes acquisition of extra CT-images and manual scoring unnecessary. These results are therefore more directly applicable in clinical practice because only already available information from PET/CT is used. The clear benefit of our method is the reduction in false negative test results, since this would be of great importance for patientcare. However, the overall performance of our combined model showed slight reduction of diagnostic performance compared to a model with only MPI (AUC 0.74 vs 0.83). This is due to the increased number of false positive test results leading to poor specificity. Special caution for the interpretation of a newly positive test results after addition of CAC scores is therefore necessary. Future research should focus on this.

4.3. Strengths and limitations

This study was a single center retrospective analysis on perfusion imaging data. Patients with a previous CABG were excluded because MPI often yields positive results just above the level of the anastomosis and correlation with epicardial coronary artery disease is notoriously complicated in post CABG patients. We did not use core lab evaluations for the coronary angiography results, however we did perform QCA analysis on all lesions. As in all MPI studies with CAG as reference, there will be referral bias. We observed an increase of false positive tests as a result of the decrease in false negative test results, which has an impact on the specificity. Most patients with negative tests results are not referred for angiography, this might have induced biased assessment of the true negative fraction. However future studies should focus on reducing the amount of false positive test results to make this method trustworthy in clinical practice.

There are several strengths of this study. This is real world data from a center with high numbers of rubidium PET imaging. To our knowledge this is the largest study on the simultaneous assessment of ischemia and CAC scores on MPI images for the detection of obstructive CAD. Another important strength is the algorithm which is used to calculate the CAC scores which is fully automated and easily applicable to data that is already acquired for another purpose. Currently this software is not (yet) free available, however it is possible to purchase a license and use the algorithm.

5. Conclusion

We found that automatically derived coronary calcium scores simultaneously collected with MPI improve the diagnostic accuracy of MPI for the detection of obstructive CAD in patients with suspected myocardial ischemia without previous coronary revascularization.

6. Disclosures

None of the authors had a relationships with the industry to declare.

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Supplementary data

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