Computed tomography coronary angiography : from quantification of coronary atherosclerosis to risk stratification of patients

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Chapter 7

Automated quantitative coronary computed tomography correlates of myocardial ischaemia on gated myocardial perfusion SPECT

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Abstract

Purpose: Automated software tools have permitted more comprehensive, robust and reproducible quantification of coronary stenosis, plaque burden and plaque location of coronary computed tomography angiography (CTA) data. The independent association between these quantitative CTA parameters and the presence of myocardial ischemia has not been explored. The aim of the present investigation was to evaluate the association between quantitatively assessed parameters of coronary artery lesions (QCT) on CTA and the presence of myocardial ischemia on gated myocardial perfusion single-photon emission computed tomography (SPECT).

Methods: Forty patients (mean age 58.2±10.9 years, 27 men) with known or suspected CAD who had undergone multi-detector row CTA and gated myocardial perfusion SPECT within 6 months were included. From CTA datasets, vessel and lesion-based visual analysis was performed. Consecutively, lesion-based QCT was performed to assess plaque length, plaque burden, percentage lumen area stenosis and remodeling index. Subsequently, the presence of myocardial ischemia was assessed using the summed difference score (SDS ≥2) on gated myocardial perfusion SPECT.

Results: Twenty-five (62.5%) patients showed myocardial ischemia in 37 vascular territories. Quantitative significant stenosis and quantitative assessment of lesion length were independently associated with myocardial ischemia (OR 7.72 [2.41 – 24.7], P <0.001 and OR 1.07 [1.00 – 1.45], P = 0.032, respectively) after correcting for clinical variables and visually assessed significant stenosis. The addition of quantitative significant stenosis (χ^2 = 20.7) and quantitative assessment of lesion length (χ^2 = 26.0) to the clinical variables and the visual assessment (χ^2 = 5.9) had incremental value in the association with myocardial ischemia.

Conclusion: Coronary lesion length and quantitative assessed significant stenosis were independently associated with myocardial ischemia. Both quantitative parameters have incremental value over baseline variables and visual significant stenosis. Potentially, QCT can refine assessment of CAD, which may be of potential use for identification of patients with myocardial ischemia.

Introduction

Computed tomography angiography (CTA) allows evaluation of coronary artery stenosis with high image quality and diagnostic accuracy when compared to invasive coronary angiography.[1-4] As CTA provides detailed information on coronary anatomy and stenosis, it has been proposed as a suitable rule-out test for the evaluation of low to intermediate risk patients with suspected coronary artery disease (CAD) [5]. Although the degree of coronary luminal narrowing is of importance in patients with CAD, previous studies have shown that coronary stenosis is not an accurate predictor of myocardial ischemia.[6] It has been previously reported that in 50% of patients with a significant stenosis, which was defined as ≥50% luminal narrowing on CTA, myocardial ischemia was not detected on myocardial perfusion single photon emission computed tomography (SPECT).[6] Beyond coronary stenosis, additional coronary plaque parameters such as lesion extent, plaque composition as well as plaque location have shown to be significantly associated with myocardial ischemia.[7, 8] However, these parameters are not systematically assessed in clinical practice and the assessment of CAD is mostly based on quantification of coronary artery calcium score and visual estimation of the luminal narrowing. Recent advances in post-processing MDCT data software have permitted automated quantification of coronary stenosis severity and plaque characteristics.[9] This automated software provides good diagnostic accuracy and reproducibility to assess significant coronary artery stenosis. Currently, the relation between quantitative CTA (QCT) derived parameters and the presence of myocardial ischemia on SPECT data is unknown. Accordingly, the present study aimed to assess the association between QCT parameters and presence of myocardial ischemia as assessed with myocardial perfusion SPECT.

Methods

Patient population

Forty patients from an ongoing clinical registry who were referred for multi-detector row CTA and stress-rest gated myocardial perfusion SPECT (performed within 6 months) were included. Only patients with sufficient image quality of both modalities were selected. Cardiovascular risk factors and cardiac medication were derived from medical record data. Known CAD was defined as a history of myocardial infarction, or evidence of CAD on previously performed diagnostic tests. Patients who had undergone prior percutaneous coronary intervention or coronary artery bypass graft surgery were excluded. Patients with atrial fibrillation, renal insufficiency (glomerular filtration rate <30 mL/min), known allergy to iodine-containing contrast agents or

pregnancy were also excluded. Also, patients with cardiac events or coronary revascularization during the time elapsed between cardiac CTA and myocardial perfusion SPECT were excluded from further analysis.

The number of coronary plaques per vascular territory along with their location and characteristics were assessed visually from CTA. Subsequently, a novel automated post-processing imaging algorithm was applied which permits quantitative assessment of CTA datasets. The most severe coronary lesion was identified in each coronary artery and QCT was performed to assess coronary stenosis parameters as described in Table 1.

Stress-rest myocardial perfusion SPECT with ^{99m}technetium tetrofosmin was performed to assess the extent and location of myocardial ischemia. Myocardial ischemia was defined as a summed difference score (SDS) of ≥2.[10] Clinical data were prospectively entered into the departmental Cardiology Information System (EPD-Vision©, Leiden University Medical Center, the Netherlands) and retrospectively analyzed. The Institutional Review Board of the Leiden University Medical Center approved this retrospective evaluation of clinically collected data, and waived the need for written informed consent.

Table 1: QCT derived parameters and their corresponding definitions.

QCT parameter	Definition
Lesion length (mm)	The distance between the proximal and distal ends of the coronary lesion
Mean plaque burden	The sum of ((vessel wall area – lumen area) / vessel wall area) per slice / number of slices
Minimal and maximal plaque thickness (mm)	The minimal and maximal distance between the vessel wall and the lumen
Minimal Lumen Area (MLA) (mm^2)	The minimal lumen area at the point of maximal obstruction
Percentage lumen area stenosis at the level of the MLA (%)	1 - (MLA/corresponding reference lumen area)
Minimal lumen diameter (mm)	The minimal lumen diameter (mm) at the point of maximal obstruction determined by the MLA
Diameter stenosis (%)	The percentage diameter stenosis at the point of maximal obstruction determined by the MLA
Plaque burden at the MLA	((vessel wall area – lumen area) / vessel wall area) x 100% at the level of the MLA
Eccentricity index at the level of the MLA	(maximum plaque thickness– minimum plaque thickness) / maximum plaque thickness
Remodeling index at the level of the MLA	Vessel wall area / corresponding reference vessel wall area at the level of the MLA), in which positive remodeling was defined as a remodeling index >1.0 [32]

Cardiac CTA examination

Cardiac CTA imaging was performed using either a 64-detector row helical scanner (n=24) (Aquilion 64, Toshiba Medical Systems, Otawara, Japan) or a 320-detector row volumetric scanner (n=16) (Aquilion ONE, Toshiba Medical Systems, Otawara, Japan).

Patients with a heart rate above 65 beats/min received 50 or 100 mg metoprolol orally one hour before imaging, unless contraindicated. A non-contrast enhanced and contrast-enhanced scan was performed. Reconstructed images were transferred to a remote dedicated workstation with post-processing software (Vitrea FX 1.0, Vital Images, Minnetonka, MN, USA). The non-enhanced scans were used to assess the total amount of coronary artery calcium score according to the Agatston approach [11]. CTA datasets were evaluated according during routine clinical practice independent of the quantitative CTA analysis. Image quality of the CTA scans was classified as: (1) good image quality (scans without motion artifacts), (2) moderate image quality (scans with motion artifacts or increased image noise) and (3) poor image quality (non-diagnostic scans); the last were excluded from the analysis. The number and location of atherosclerotic plaques per vascular territory and plaque morphology were visually evaluated from CTA data sets. Significant coronary obstruction was defined as ≥50% luminal narrowing. Atherosclerotic plaques were morphologically classified as non-calcified (lesions with lower density compared to contrast-enhanced lumen), calcified (lesions with high density) or mixed (lesions having elements of both non-calcified and calcified lesions).

Quantitative computed tomography coronary angiography

Dedicated software (QAngioCT Research Edition, Medis Medical Imaging Systems, Leiden, the Netherlands) was used for automated quantification of all coronary lesions.[9] The software automatically displays the centerline along the vessel and detects the contours of the lumen and vessel wall while allowing the observer to manually correct them if needed. First, a fast vessel-tracking algorithm was used to obtain the 3-dimensional centerline (ranging from the proximal to distal marker) of the coronary artery. Based on this centerline, a straightened multi-planar reformatted (MPR) volume of the segment of interest was created. Consecutively, the lumen border contours and vessel wall borders were detected according to methods described previously.[9] The approach uses spatial first- and second-derivative gradient filters in combination with knowledge of the expected CT intensity values in the arteries; therefore, this method is insensitive to differences in attenuation values between data sets. Automated quantitative processing steps were independent from viewing settings. Next, automated quantification of each coronary lesion was performed. For each coronary lesion, reference lines for both lumen and vessel wall were generated using proximal

and distal non-diseased, non-bifurcated reference regions. The mean lumen or vessel wall area of these regions was used to define the reference slope for lumen and vessel wall contours, respectively. The reference lines for lumen and vessel wall represent an estimate of the normal proximal-to-distal tapering of the coronary artery. The minimal lumen area (MLA), the proximal start of the coronary lesion and the distal end of coronary lesion were automatically defined using the detected lumen contours and the difference with the normal tapering of the artery. A number of QCT parameters, listed in Table 1, were derived for each coronary lesion. In addition to coronary vessels with atherosclerotic lesions, automated quantification of non-diseased coronary vessels was performed in the mid part of the coronary vessel, which was used as the best estimate of coronary luminal narrowing per non-diseased coronary artery. Lesions in diagonal branches were allocated to LAD, lesion in intermediate (IM) branch or marginal (OM) branch were allocated to CX. The reproducibility of QCT has been reported previously,[9] showing good reproducibility of QCT for assessment of minimal lumen area and lumen area stenosis.

Stress-rest gated SPECT

Gated myocardial perfusion SPECT with ^{99m}technetium tetrofosmin (500 MBq, MYOVIEW, General Electric Healthcare, United Kingdom) was performed according to a 2-day stress-rest protocol. In patients who were able to exercise, a symptom-limited bicycle test was performed. In patients unable to exercise, a pharmacologic stress test was performed with either adenosine or dobutamine infusion. Injection of the radiopharmaceutical was done at peak exercise; in the third minute of pharmacological stress induction for adenosine or at the maximum calculated target heart rate for dobutamine. Data-acquisition was performed with a triple-head SPECT camera system (GCA 9300/HG; Toshiba Corporation, Tokyo, Japan), equipped with low-energy high-resolution collimators, 45 minutes after injection of the radiopharmaceutical. A 20% window was used around the 140-keV energy peak of technetium-99m, after which the SPECT data were stored in a 64x64 matrix.

Post-processing of stress- and rest-SPECT datasets was performed using previously validated automated software.[12] Data-reconstruction was performed in vertical and horizontal long- and short-axis views perpendicular to the heart axis. The myocardial segments were assigned to the different perfusion territories using a 20-segment model.[13] Each segment was visually scored by an experienced observer (AJS) according to the standard scoring scale of 0 to 4 (normal, mild, moderate, severe reduction or absence of tracer uptake).[13, 14] To calculate the summed stress score (SSS) and the summed rest score (SRS), the total segmental perfusion scores during stress and rest were added, respectively. The summed difference score (SDS) was calculated as the

difference between the summed stress score and the summed rest score. Myocardial ischemia was defined as an SDS ≥ 2.[10]

On a vessel basis, the presence of myocardial ischemia was assessed and allocated to the corresponding vascular territory as previously described.[15] Accordingly, myocardial ischemia of the anterior and septal wall was allocated to lesions in the left anterior descending coronary artery (LAD), whereas ischemia in the lateral wall was allocated to lesions in the left circumflex coronary artery (LCX). Furthermore, myocardial ischemia in the (postero) inferior wall was assigned to lesions in the right coronary artery (RCA).

Statistical analysis

For reasons of uniformity, summary statistics for all continuous variables were presented as mean ± standard deviation (SD), whereas categorical variables were presented as frequencies and percentages. Vessel-based analysis was performed based on the most severe lesion per vessel according to the quantitatively assessed percentage lumen area stenosis. Independent-samples T tests were used to compare QCT parameters between patients with and without myocardial ischemia on SPECT. The agreement between both visual and quantitative assessment of significant coronary stenosis and SPECT was evaluated using the weighted kappa (k) statistics. Excellent, fair-to-good and poor agreement were defined by a k-value of > 0.75, between 0.4 and 0.75, and < 0.4, respectively.[16] To evaluate the association between baseline characteristics, visual CTA parameters, QCT parameters and the presence of myocardial ischemia, multivariate regression analyses were performed. Myocardial ischemia was introduced as dependent variable. Relevant baseline clinical variables were entered into the first model. Variable selection was performed using a backward conditional method (entry, 0.05; removal, 0.10). Three nested models were subsequently created by introducing separately the following variables: visual significant stenosis (model 2), quantitative significant stenosis (model 3) and quantitative assessed lesion length (model 4). For each variable in the model, an odds ratio (OR) with 95% confidence interval (CI) was calculated. The incremental value of the QCT parameters over clinical risk variables and visual assessed stenosis degree was assessed by comparing the global χ^2 values. The likelihood-ratio chi-square test was used to assess the significance of the incremental χ^2 values. All statistical tests were two-sided and a P-value <0.05 was considered to be statistically significant. All statistical analyses were performed with SPSS software (Version 20.0, SPSS Inc., Chicago, Illinois).

Results

Patient population

A total of 40 patients (58.2 ± 10.9 years, 27 men) with known (n=16) or suspected (n=24) CAD were included. Of these patients, 16 (40%) presented with atypical chest pain, 12 (30%) with typical chest pain, the remaining 12 (30%) patients had diabetes and were evaluated because of an increased cardiac risk profile. The mean duration between cardiac CTA and gated myocardial perfusion SPECT examinations was 39.9 ± 42.2 days (median 33 days, interquartile range 10-52 days). Patients remained clinically stable and no acute coronary events were recorded between evaluations. The clinical characteristics of the patients are listed in Table 2.

Computed tomography coronary angiography

Visual CTA.

The mean coronary artery calcium score was 451±1490. In the overall patient population (n=40), 83 coronary arteries showed atherosclerosis and a total of 162

Table 2. Patient characteristics.

Baseline characteristics	n = 40
Age (years)	58.2 ± 10.9
Male	27 (67.5%)
Known CAD	16 (40.0%)
Cardiovascular risk factors	
Hypertension†	20 (50.0%)
Hypercholesterolemia‡	15 (37.5%)
Diabetes mellitus	21 (52.5%)
Family history of CAD*	17 (42.5%)
Smoking	15 (37.5%)
Body Mass index ≥30 kg/m2.	6 (15.0%)
Calcium score	450 ± 1490 28 (0-8730)
Left ventricular ejection fraction	61 ± 13

Data are represented as mean ± SD, median(range) or as number and percentages of patients.
†Defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or the use of antihypertensive medication.
‡Serum total cholesterol ≥230 mg/dL or serum triglycerides ≥200 mg/dL or treatment with lipid lowering drugs.
*Defined as the presence of coronary artery disease in first-degree family members at <55 years in men and <65 years in women.
Abbreviations: CAD, coronary artery disease

coronary lesions were identified. Visual CTA analysis showed 57 (35%) non-calcified lesions, 71 (44%) mixed lesions and 34 (21%) calcified lesions. In total, 25 coronary arteries contained a visually assessed significant stenosis of ≥50% luminal narrowing.

Quantitative CTA.

QCT was performed in all 162 lesions to assess quantitative stenosis parameters as described in Table 1. Subsequently, in the 83 coronary arteries with atherosclerosis, the most severe lesion per main vascular territory (using the quantitatively assessed percentage lumen area stenosis) was determined. In Table 3 the results of the quantitative analyses of all coronary lesions and the most severe lesion per artery is demonstrated. In addition, in the remaining 37 non-diseased coronary arteries, QCT analysis was performed in the mid part of the vessel, which was used as a representative of the coronary artery. In total, 45 coronary arteries contained a quantitative assessed significant stenosis of ≥50% luminal narrowing (defined according the percentage area stenosis).

Stress-rest gated myocardial perfusion SPECT

Gated myocardial perfusion SPECT showed a mean SRS of 2.8 ± 3.9, a mean summed stress score of 5.7 ± 6.3, and a mean SDS of 3.8 ± 4.9. Myocardial ischemia (SDS of ≥2) was observed in 25 (62.5%) patients. Using a 20-segment model, myocardial ischemia was present in 31% (n=37) of the 120 vascular territories. The remaining 69% (n=83) vascular territories showed no ischemia. A comparison was made between vascular territories with ischemia versus vascular territories without ischemia. In vascular territories showing myocardial ischemia, lesion length, percentage lumen area stenosis, percentage lumen diameter stenosis, mean plaque burden and maxi-

Table 3. Quantitative analysis of coronary lesions.

QCT parameter	All coronary lesions (n = 162)	Most severe lesion per artery (n=83)
Lesion length (mm)	12.10 ± 8.99	12.48 ± 9.14
Mean plaque burden (%)	76.12 ± 7.78	76.90 ± 7.92
Maximal plaque thickness (mm)	2.33 ± 0.71	2.39 ± 0.77
MLA (mm^2)	2.97 ± 2.19	2.70 ± 1.81
Percentage lumen area stenosis (%)	47.80 ± 18.65	52.76 ± 19.67
Minimal lumen diameter (mm)	1.84 ± 0.64	1.76 ± 0.60
Percentage diameter stenosis (%)	29.10 ± 13.79	32.90 ± 14.96
Plaque burden at the MLA (%)	82.30 ± 8.39	83.29 ± 8.59
Eccentricity index at the level of the MLA	0.60 ± 0.15	0.60 ±0.16
Remodeling index at the level of the MLA	1.05 ± 0.21	1.07 ± 0.23

Abbreviations: MLA, minimal lumen area

mal plaque thickness were significantly higher when compared to vascular territories without myocardial ischemia (Table 4).

Agreement between visual significant stenosis and quantitative assessed stenosis versus myocardial ischemia

On a vessel-based analysis, the number of significant culprit coronary lesions (≥50% luminal narrowing) was significantly higher using QCT as compared to visual CT analysis (45 (37.5%) vs. 25 (20.8%), P<0.001). Importantly, myocardial ischemia was present in 22 (48.9%) of those significant lesions assessed with QCT (k = 0.30, P=0.001), whereas ischemia was only present in 9 (36.0%) of the significant lesions visually assessed (k = 0.06, P=0.53). Figure 2 represents an example of a female patient with an obstructive lesion in the LAD coronary artery and myocardial ischemia on gated myocardial perfusion SPECT.

Independent association between quantitative coronary CTA parameters and myocardial ischemia on gated myocardial SPECT

To evaluate the independent association between visual CTA, quantitative parameters and myocardial ischemia, 4 nested multivariate models were created. In model 1,

Table 4. Vessel based comparison of visual and quantitative CTA parameters between coronary arteries of vascular territories with and without myocardial ischemia.

	Ischemia (37 vascular territories)	No ischemia (83 vascular territories)	*P-value*
Visual CTA (per vessel (n=120))			
No. of lesions[o]	1.76 ± 1.57	1.17 ± 1.19	0.026
No. of bifurcation lesions[o]	0.46 ± 0.61	0.22 ± 0.44	0.015
No. of non-calcified lesions[o]	0.59 ± 0.72	0.42 ± 0.65	0.195
No. of mixed lesions[o]	0.84 ± 1.32	0.45 ± 0.78	0.045
No. of calcified lesions[o]	0.32 ± 0.71	0.30 ± 0.66	0.863
QCT parameters (per vessel (n=120))			
Lesion length (mm)[‡]	13.41 ± 12.09	6.68 ± 7.32	<0.001
Mean plaque burden (%)[‡]	75.27 ± 11.59	70.98 ± 9.85	0.039
Max. plaque thickness (mm)[‡]	2.31 ± 1.08	1.75 ± 0.83	0.003
Lumen area stenosis (%)[‡]	48.40 ± 27.81	35.04 ± 25.35	0.011
Lumen diameter stenosis (%)[‡]	30.94 ± 20.00	21.17 ± 16.87	0.007
Eccentricity index[‡]	0.54 ± 0.14	0.54 ± 0.18	0.846
Remodeling index[‡]	1.10 ± 0.22	1.03 ± 0.20	0.406

Data are represented as mean ± SD. [o]Total number of lesions, bifurcation lesions, non-calcified, mixed and calcified lesions per vascular territory. [‡]Results of the selected most severe lesion per vascular territory.

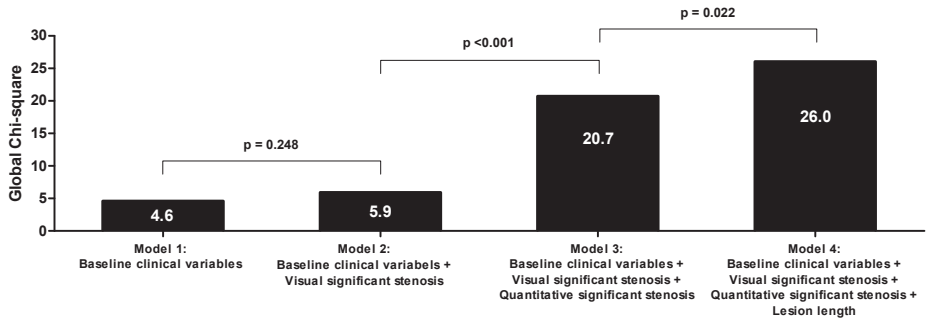

Figure 1. Bar graph of the multivariable models.
The bar graph shows the incremental value of quantitative CT parameters over visual CT in the association with myocardial ischemia on gated myocardial perfusion SPECT on a vessel-basis (n=120). The presence of quantitative significant stenosis (≥50% percentage area stenosis) showed a significant incremental value over conventional clinical risk variables and visual assessed significant stenosis (≥50% stenosis). Furthermore, lesion length provided a significant incremental value over both clinical risk variables and the presence of a quantitative significant stenosis (≥50% percentage area stenosis.

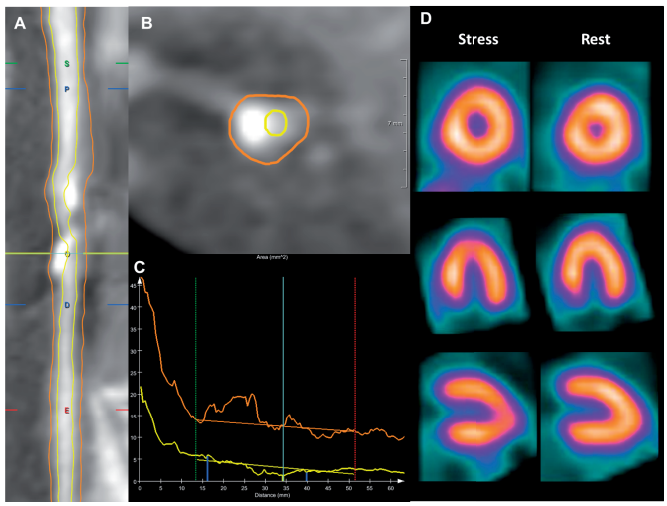

Figure 2. An example of a 53 year-old female patient with an obstructive lesion in the left anterior descending (LAD) coronary artery.
The quantitative computed tomography (QCT) processing steps of the culprit lesion are illustrated below. At first, automated QCT was used to detect both lumen (yellow) and vessel wall (orange) contours. Longitudinal lumen and vessel wall contours are shown in panel A, whereas transversal lumen and vessel wall contours at the level of the minimal lumen area (MLA) are shown in panel B. Quantification of the culprit lesion was performed using proximal (green) and distal (red) reference markers as well as lumen (yellow) and vessel wall (orange) reference lines, as illustrated in panel C. Stress-rest gated myocardial perfusion SPECT is shown in panel D. The patient had corresponding myocardial ischemia in the LAD vascular territory on gated myocardial perfusion SPECT. For this patient, summed rest score was 0 and summed stress score was 2, resulting in a summed difference score of 2. QCT showed a lesion length of 23.7 mm, percentage lumen area stenosis of 69.6% and a mean plaque burden of 81.5%.

clinical baseline variables were entered using backward selection. Subsequently, the presence of significant coronary stenosis as assessed with visual CTA was introduced in model 2 and the presence of significant coronary stenosis and lesion length assessed with QCT were included in models 3 and 4, respectively. The results of the 4 nested multivariate models are described in Table 5. Visual CTA assessment of luminal narrowing was not independently associated with the presence of ischemia (OR=1.84, P=0.246). In contrast, the presence of a quantitative assessed significant stenosis and lesion length were independently associated with the presence of myocardial ischemia on gated myocardial SPECT when added to relevant clinical variables (OR=7.36, P<0.01 and OR=1.07, P=0.028).

Furthermore the incremental contribution of all parameters was assessed as shown in Figure 1. Visual significant stenosis provided no significant contribution to the model over relevant baseline risk factors (χ^2 change from 4.6 in model 1 to 5.9 in model 2, P=0.248). The introduction of quantitative significant stenosis in model 3 provided a significant increase in χ^2 over model 1 (from 15.9 to 20.8, P<0.01). Additionally, introducing lesion length into model 4 provided significant increment over quantitative stenosis (increase in model χ^2 = 4.2, P=0.022).

Discussion

The present study demonstrated that quantitative derived CTA parameters are associated with the presence of myocardial ischemia on gated myocardial perfusion SPECT. The QCT derived parameters, coronary lesion length, mean plaque burden, maximal plaque thickness, percentage lumen area stenosis, and presence of significant coronary stenosis (≥50% percentage lumen area stenosis) were significantly higher in coronary artery lesions of vascular territories presenting with myocardial ischemia (Table 4). Furthermore, both coronary lesion length and the presence of quantitative significant coronary stenosis showed a significant incremental value in the association with myocardial ischemia independent of conventional clinical risk variables and the presence of a visual assessed significant stenosis (≥50% percentage lumen area stenosis).

CTA has a high diagnostic accuracy for the non-invasive detection of coronary atherosclerosis, but a large percentage of lesions are not associated with ischemia on SPECT, since it is considered that non-obstructive coronary stenoses do not induce ischemia.[17] However, various studies have shown that myocardial ischemia is not only dependent on the presence of obstructive CAD, pointing to other potentially important plaque characteristics.[18-20] It has also been reported that diffuse atherosclerosis contributes to myocardial ischemia,[21, 22] in which plaque extent as well as the

Table 5. Multivariate analysis of correlation between, clinical risk factors, visual assessed significant stenosis, quantitative CT parameters and myocardial ischemia on gated myocardial perfusion SPECT on a vessel-basis (n=120).

Model 1: Baseline clinical variables			**Model 2: Baseline clinical variables + visual significant stenosis**			**Model 3: Baseline clinical variables + visual significant stenosis + quantitative significant stenosis**			**Model 4: Baseline clinical variables + visual significant stenosis + quantitative significant stenosis + lesion length**		
	OR (95% CI)	P-value		OR (95% CI)	P-value		OR (95% CI)	P-value		OR (95% CI)	P-value
Age	0.97 (0.94 ; 1.02)	0.219	Age	0.97 (0.92 ; 1.01)	0.128	Age	0.93 (0.88 ; 0.98)	0.010	Age	0.92 (0.87 ; 0.98)	0.005
Family History	0.44 (0.18 ; 1.05)	0.065	Family History	0.42 (0.17 ; 1.02)	0.055	Family History	0.41 (0.16 ; 1.09)	0.074	Family History	0.38 (0.14 ; 1.05)	0.062
Diabetes Mellitus	0.55 (0.23; 1.35)	0.194	Diabetes Mellitus	0.49 (0.19 ; 1.23)	0.127	Diabetes Mellitus	0.39 (0.14 ; 1.08)	0.071	Diabetes Mellitus	0.35 (0.12 ; 1.05)	0.060
$\chi^2 = 4.6$			Visual significant stenosis	1.84 (0.66 ; 5.18)	0.246	Visual significant stenosis	0.95 (0.30 ; 3.04)	0.936	Visual significant stenosis	1.08 (0.33 ; 3.57)	0.898
			χ^2= 5.9 p =0.248			Quantitative significant stenosis	7.36 (2.45 ; 22.09)	<0.001	Quantitative significant stenosis	3.83 (1.12 ; 13.26)	0.034
						$\chi^2 = 20.7$ p =<0.0001			Lesion length	1.07 (1.01 ; 1.13)	0.028
									χ^2= 26.0 p =0.022		

number of diseased segments have been identified as important parameters for the prediction of myocardial ischemia.[8]

In this perspective, cardiac CTA represents a useful non-invasive imaging technique as it provides information beyond coronary obstruction, including plaque composition, plaque burden, lesion length as well as plaque remodeling. These plaque characteristics have shown to be independently associated with the extent, severity and reversibility of myocardial ischemia,[23] even showing an incremental predictive value for myocardial ischemia over the presence of obstructive CAD.[8]

Quantification of plaque parameters including lesion length, degree of luminal obstruction, plaque burden and remodeling could be more accurate than visual assessment to evaluate the coronary atherosclerosis burden and the risk of ischemic events. In addition, quantitative assessment may provide a more reliable and reproducible approach than visual estimation to evaluate and follow-up patients with coronary atherosclerosis.

Previous attempts in quantifying coronary stenosis using either manual[24] or semi-automated[25,26] approaches have been suboptimal due to the large variability introduced by manual interference as well as difficulties in quantifying heavily calcified lesions.

Thus far, the feasibility of a novel dedicated algorithm for automated quantification of stenosis severity on CTA has been demonstrated in comparison with quantitative coronary angiography showing improved diagnostic accuracy for assessment of significant coronary lesions compared to visual CTA analysis [27]. Furthermore, QCT showed good correlations with quantitative intravascular ultrasound (IVUS) for assessment of coronary stenosis.[9] Although the feasibility of automated QCT analyses has been demonstrated, no study has currently been performed evaluating the value of QCT in the association with the presence of myocardial ischemia on myocardial perfusion SPECT. The current study is the first study that has evaluated the correlates of QCT parameters, derived by a novel algorithm for automated quantification of coronary lesions, with myocardial ischemia. Vessel-based analysis showed that vascular territories with ischemia had a significantly higher number of coronary lesions, bifurcation lesions as well as mixed lesions. QCT plaque parameters including, lesion length, mean plaque burden, maximal plaque thickness, percentage lumen area stenosis and percentage lumen diameter stenosis were significantly higher in vascular territories showing ischemia as compared to vascular territories without ischemia. These results indicate the presence of a significant association between quantitatively derived plaque parameters, representing the extent and severity of atherosclerotic lesions, and the presence of myocardial ischemia. Furthermore, in the present study these quantitatively derived plaque parameters were significantly associated with the presence of myocardial ischemia. Once corrected for clinical

risk variables and visually assessed stenosis degree, both lesion length and the presence of a quantitatively assessed significant stenosis were independently associated with myocardial ischemia. These results are in line with previous studies showing a significant association angiographically assessed lesion length and stenosis severity with myocardial infarction.[28] Additionally, the presence of quantitative significant coronary stenosis (with a cutoff percentage area stenosis of ≥50% luminal narrowing) showed incremental value in a nested multivariate model using myocardial ischemia as the endpoint, whereas, the visual assessment of significant lesions (≥50% luminal narrowing) did not. This underlines the hypothesis that QCT provides a more accurate lesion analysis as compared to a visual assessment of the CTA images.

Furthermore, lesion length as a representative of diffuse atherosclerosis provided a significant incremental value over the clinical risk variables, visually assessed significant stenosis and quantitative significant stenosis. These results are supported by earlier findings that the additive effect of multiple mild stenoses in series eventually causes perfusion defect.[21] The increase in lesion length represents a more extensive atherosclerotic involvement of the coronary artery, which may lead to considerable more myocardial ischemic damage than might be the case with a short localized obstructive lesion.

In addition, the number of quantitatively assessed significant coronary stenosis was significantly higher compared to the number of visually assessed significant coronary stenosis. Even though the correlation between the presence of myocardial ischemia and stenosis degree assessed using either a visual approach or QCT was poor, there was a significantly improved association between QCT and myocardial ischemia when compared to visual CTA and myocardial ischemia. This discrepancy between visual and QCT for assessment of significant coronary lesions may indicate the importance of using a more accurate quantitative approach for CTA. Accordingly, QCT allows an improved and comprehensive evaluation of coronary plaques which may cause myocardial ischemia.

Limitations

Some limitations need to be considered. In the current study, the prevalence of myocardial ischemia was relatively low on a vessel basis. It would have been preferred to evaluate the performance of QCT in a larger population with higher prevalence of ischemia. However, since CTA is generally performed in low to intermediate risk patients, the present cohort is representative for a general CT population. In addition, QCT was only used in CTA data sets with good or moderate image quality. Furthermore, the present study was subject to selection bias caused by the exclusion criteria for CTA and SPECT. Finally, patients underwent 64- or 320-slice CTA, and currently the diagnostic accuracy of these two techniques has not been evaluated

in a head-to-head comparison; on the other hand, individual 64- and 320-slice CTA studies reported similar diagnostic accuracy for detection of CAD[5].

Clinical implications

Recent observations have emphasized the discrepancy between coronary artery stenosis (severity) and the presence of ischemia. As recently demonstrated in the FAME trials,[29, 30] fractional flow reserve (FFR) guided coronary revascularization is superior to angiographic stenosis assessment. Also, the DEFACTO trial[31] demonstrated that assessment of FFR from the CTA images provides incremental value over stenosis degree assessment. At present, it is unknown if either stenosis severity or ischemia has the largest influence on prognosis. Possibly, additional characteristics of coronary lesions other than stenosis degree are more related to the presence of myocardial ischemia. As QCT provides an accurate and comprehensive assessment of coronary plaques together with an improved association with myocardial ischemia when compared to visual CT, QCT can be used to improve the diagnostic value of cardiac CTA. Accordingly, it may result in improved risk stratification and less subsequent testing. It has been shown that non-invasive coronary angiography with cardiac CTA allows detection of CAD (i.e. the detection of hemodynamically non-significant CAD) at a much earlier stage than gated myocardial perfusion SPECT. Besides, a normal myocardial perfusion scan does not exclude CAD.[17] Potentially, QCT can facilitate early detection of CAD and accurate identification of patients who may have myocardial ischemia.

Conclusion

Coronary lesion length and the presence of a quantitatively assessed significant stenosis as derived from QCT are significantly correlated with myocardial ischemia on gated myocardial perfusion SPECT. Furthermore, QCT provides incremental value over CTA and baseline clinical risk factors in the association with ischemia on SPECT. Potentially, QCT can refine assessment of CAD, which may be of potential use for identification of patients with myocardial ischemia.

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