CT CORONARY ANGIOGRAPHY IN CLINICAL PRACTICE

ANNICK CARINE WEUSTINK

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CT CORONARY ANGIOGRAPHY IN CLINICAL PRACTICE

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Sometimes the heart sees what is invisible to the eye

CONTENTS

PART 1

PREFACE

CHAPTER 1

GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

GENERAL INTRODUCTION

Stable angina is a common and disabling disease with coronary artery disease (CAD) accounting for 68% of heart related deaths (1). Common risk factors for CAD include hypertension, high cholesterol levels, cigarette smoking, obesity, and a family history of heart disease. Traditionally ischemic testing include exercise ECG and stress myocardial perfusion imaging (SPECT) for the non-invasive detection of inducible ischemia. Invasive coronary angiography (ICA) is generally considered the standard of reference for the detection of significant CAD.

Cardiac multi-slice CT (MSCT) has rapidly evolved as an alternative non-invasive imaging test (2). Coronary calcium, as assessed by non-contrast enhanced CT coronary calcium score (CCS), is a marker of the presence of coronary atherosclerosis (3), but its presence does not necessarily imply the presence of a coronary stenosis.

Three large multicenter studies have demonstrated the high diagnostic performance of 64-slice CT coronary angiography (CTCA) for the detection of significant CAD in patients with stable angina (4-6). The selection of a test, however, depends not only on the diagnostic accuracy of the test, but also on other factors including pretest probability of disease, safety, costs, availability, patient's convenience and the use of radiation.

The clinical utility of CTCA in the diagnosis of significant CAD remains to be established. There is an ongoing debate whether management of patients with stable angina should be primarly based on anatomical or functional imaging. There is a well known dissociation between the functional relevance of a coronary obstruction (ischemia) and the anatomical severity of a coronary stenosis that is heamodynamically significant (7-8). CTCA is moderately predictive for indicating the functional significance of a lesion, but is highly predictive for exclusion of significant CAD. There is wide consensus that 64-slice CTCA may serve as a reliable gatekeeper test to ICA.

Limitations of 64-slice CTCA include insufficient spatial resolution to reduce blooming artefacts in severly calcified segments or coronary stents; insufficient temporal resolution to aqcuire motion free images in patients with arrythmias; and a relative high patient dose (5-15 mSv). Before CTCA may replace ICA, the technique needs further improvement with better spatial and temporal resolution at low radiation exposure.

OUTLINE OF THE THESIS

The diagnostic performance of dual-source CTCA for the detection of significant CAD is evaluated in Part 2 in symptomatic patients without known CAD (Chapter 2 and 3) and in patients after percutaneous coronary intervention (Chapter 4) or coronary bypass surgery (Chapter 5).

Part 3 emphasizes on the clinical application of 64-slice CTCA in relation to available noninvasive diagnostic tests in patients presenting with stable angina. The diagnostic performance of exercise ECG with CTCA was compared in 334 patients, and SPECT with CTCA in 61 patients for the detection of obstructive CAD (Chapter 6). The accuracy and clinical utility of stress testing and CTCA for identifying patients who require invasive coronary angiography was investigated in relation to pretest probability (Chapter 7). The incremental value of clinical evaluation, bicycle stress testing and CT coronary calcium score was evaluated and a clinical probability score for restrictive referral to CTCA was developped (Chapter 8).

Three manuscripts are provided in Part 4 which describe optimization of dual-source spiral CT scan protocols using electrocardiographic (ECG) pulsing. The optimal width and timing of the ECG pulsing windows in relation to heart rate, image quality, and radiation exposure is provided (Chapter 9). The following chapter describes the effects of standard and optimal ECG pulsing on diagnostic performance, radiation dose, and cancer risk (Chapter 10). The impact of heart rate frequency and variability on radiation exposure, image quality, and diagnostic performance using adaptive ECG pulsing is evaluated (Chapter 11).

Part 5 provides a current and future perspective on CTCA. The role of CTCA in stable patient management based on clinical experience and performed studies is described and alternative diagnostic testing algorithms using CTCA are presented (Chapter 12). Finally, future directions of CTCA are discussed (Chapter 13).

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PART 2

DIAGNOSTIC PERFORMANCE OF CT CORONARY ANGIOGRAPHY

CHAPTER 2

RELIABLE HIGH-SPEED CORONARY COMPUTED TOMOGRAPHY IN SYMPTOMATIC PATIENTS

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ABSTRACT

OBJECTIVES: Our objective was to prospectively evaluate the diagnostic performance of the high-speed dual-source computed tomography scanner (DSCT), with an increased temporal resolution (83 ms), for the detection of significant coronary lesions (≥ 50% lumen diameter reduction) in a clinically wide range of patients.

BACKGROUND: Cardiac motion artifacts may decrease coronary image quality with use of earlier computed tomography scanners that have a limited temporal resolution.

METHODS: We prospectively studied 100 symptomatic patients (79 men, 21 women, mean age 61 ± 11 years) with atypical (18%) or typical (55%) angina pectoris, or unstable coronary artery disease (27%) scheduled for conventional coronary angiography. Mean scan time was 8.58 ± 1.52 s. Mean heart rate was 68 ± 11 beats/min. Quantitative coronary angiography was used as the standard of reference. Irrespective of image quality or vessel size, all segments were included for analysis.

RESULTS: Invasive coronary angiography demonstrated no significant disease in 23%, single-vessel disease in 31%, and multivessel disease in 46% of patients; 1,489 coronary segments, containing 220 significant (14.8%) stenoses, were available for analysis. Sensitivity, specificity, and positive and negative predictive values of DSCT coronary angiography for the detection of significant lesions on a segment-by-segment analysis were 95% (95% confidence interval [CI] 90 to 97), 95% (95% CI 93 to 96), 75% (95% CI 69 to 80), 99% (95% CI 98 to 99), respectively, and on a patient-based analysis 99% (95% CI 92 to 100), 87% (95% CI 65 to 97), 96% (95% CI 89 to 99), and 95% (95% CI 74 to 100), respectively.

CONCLUSIONS: Noninvasive DSCT coronary angiography is highly sensitive to detect and to reliably rule out the presence of a significant coronary stenosis in patients presenting with atypical or typical angina pectoris, or unstable coronary artery disease.

INTRODUCTION

For almost 50 years, invasive coronary angiography has been the standard of reference for diagnosing coronary artery disease. However, noninvasive coronary imaging with computed tomography (CT) has rapidly emerged, and initial experience with 4-, 16-, and 64-slice CT coronary angiography has been reported (1-13). Despite technical advances in CT technology, a substantial number of coronary segments remain unevaluable due to presence of motion artifacts and a limited image resolution, which seriously hampered clinical implementation of CT coronary angiography (4)(14).

A newly introduced dual-source computed tomography (DSCT) system, with an improved temporal resolution of 83 ms independent of patient's heart rate, allows for scanning of the coronaries without the use of prescan beta-blockers. The pitch is adapted to the heart rate, and scan times are reduced at higher heart rates. Shorter scan times allow for reduction of radiation exposure to the patient.

We now report the diagnostic performance of DSCT coronary angiography to detect or rule out significant coronary stenoses in the clinically relevant coronary tree in 100 patients with a wide spectrum of symptomatic coronary artery disease.

METHODS

STUDY POPULATION

After an initial 3-week test period during which scan protocols were optimized, we subsequently included during a 10-week period 111 symptomatic patients with atypical angina, typical angina, and unstable coronary artery disease (unstable angina or non–ST-segment elevation myocardial infarction) scheduled for conventional coronary angiography (CCA). All CT examinations were performed before CCA. Only patients in sinus heart rhythm without previous history of percutaneous coronary intervention or bypass surgery were included. Excluded were 11 patients with known allergy to iodinated contrast material (n = 1), impaired renal function (serum creatinine >120 μmol/l) (n = 5), persistent arrhythmias (n = 3), or logistic inability to perform a CT scan before CCA (n = 2). Thus, the study population comprised 100 patients (79 men, 21 women, mean age 61 ± 10.9 years; range 28 to 87 years). The institutional review board approved the study, and all patients gave informed consent.

PATIENT PREPARATION

No oral or intravenous prescan beta-blockers were administered before the scan.

SCAN PROTOCOL AND IMAGE RECONSTRUCTION

All patients were scanned using a DSCT (Somatom Definition, Siemens Medical Solutions, Forcheim, Germany). The system combines 2 arrays each consisting of an X-ray tube plus detector

(64 slices) mounted on a single gantry with an angular offset of 90° and a gantry rotation time of 330 ms. Dual source computed tomography permits spiral CT scanning of the coronary arteries with an improved temporal resolution of 83 ms using single-segment reconstruction (15).

In DSCT, radiation exposure has been reduced by the application of an additional cardiac bow-tie filter, a smaller field of vision of the second detector, and an increased pitch in higher heart rates. All patients underwent a nonenhanced CT scan for calcium scoring before DSCT coronary angiography. All patients received nitroglycerin (0.4 mg/dose) sublingually just before scanning.

Calcium scoring scan parameters were a tube current of 84 mAs/rot (maximum), and full X-ray tube current was given during 50% to 70% of the R-R interval. A single dataset was reconstructed using electrocardiogram (ECG) gating with a slice thickness of 3 mm and increment of 1.5 mm using a medium convolution kernel (B35f) during 60% of the R-R interval.

CT coronary angiography scanning parameters were as follows: two x-ray tubes, detector collimation of 32 x 0.6 mm per tube with double sampling by means of rapid alteration of the focal spot in the longitudinal direction (z-flying focal spot), rotation time of 330 msec, tube voltage of 120 kV, and full tube current of 625 mA per tube. Pitch values were adapted to heart rate after an estimation based on the last 10 heartbeats preceding the scan. And full X-ray tube current was given during 25% to 70% of the R-R interval.

The volume of iodinated contrast material (Ultravist 370 mgI/ml, Schering AG, Berlin, Germany) was adapted to the scan time. A contrast bolus (60 to 90 mgI) was injected in an antecubital vein at a flow rate of 5.5 ml/s followed by a saline chaser of 40 ml at 5.5 ml/s. A bolus tracking technique was applied to synchronize the arrival of contrast in the coronary arteries and the start of the scan.

All CT data sets were reconstructed by using a single-segment reconstruction algorithm, which resulted in a temporal resolution of 83 msec, a section thickness of 0.75 mm in 0.4-mm increments, and medium-to smooth (B26f) and sharp (B46f) convolution kernels. The resultant ranges of in- and throughplane spatial resolution were 0.6 -0.7 mm and 0.4 -0.5 mm, respectively (15). Images were reconstructed after a stepwise pattern depending on patient's heart rate during scanning. Initially, a single dataset was reconstructed during the mid- to end-diastolic phase (350 ms before the next R-wave) in patients with low heart rates (<60 beats/min), during both the mid- to end-diastolic phase and end-systolic phase (275 ms after the next R-wave) in patients with intermediate heart rates (60 to 80 beats/min), and during the end-systolic phase in patients with high heart rates (>80 beats/min).

Image quality was assessed on a per-segment level. In case of persistent coronary motion artifacts in patients with low and high heart rates, additional datasets were reconstructed in end-systolic and mid- to end-diastolic phase, respectively. If necessary, multiple datasets of a single patient were used separately in order to obtain optimal image quality of all available coronary segments.

The effective dose for DSCT coronary angiography was estimated based on Monte Carlo calculations (ImPACT, version 0.99x, St. George's Hospital, Tooting, London, United Kingdom).

QUANTITATIVE CORONARY ANGIOGRAPHY (QCA)

One experienced cardiologist, unaware of the results of DSCT coronary angiography, identified all available coronary segments using a 17-segment modified American Heart Association classification (16). All segments, irrespective of size, were included for comparison with DSCT coronary angiography, except for segments distal to a total occlusion.

Segments were classified as normal (smooth parallel or tapering borders), as having nonsignificant disease (luminal irregularities or <50% diameter stenosis), or as having significant stenoses (≥50% diameter stenosis). Stenoses were evaluated in 2 orthogonal views, and classified as significant if the mean lumen diameter reduction was ≥50% using a validated QCA algorithm (CAAS, Pie Medical, Maastricht, The Netherlands)

DSCT IMAGE EVALUATION

One experienced observer, unaware of the results of CCA, calculated total calcium scores as Agatston scores, using validated software (Syngo MMWP VE20A, Siemens, Forchheim, Germany).

One observer evaluated image quality on a per-segment level and classified as good image quality (defined as absence or presence of any image-degrading artifacts related to motion, calcification, or noise, but evaluations possible with good-to-moderate confidence), or poor (presence of image-degrading artifacts and evaluation only possible with low confidence). Irrespective of image quality, all available coronary segments (including poor image quality) were included for comparison of DSCT with CCA.

Two experienced observers, unaware of the results of CCA, scored all DSCT coronary angiography datasets. Axial views and maximum intensity projections were used to identify coronary lesions. In addition, (curved) multiplanar reconstructions were used to classify coronary lesions into significantly diseased or not. Interobserver disagreements were resolved by consensus in a joint session.

STATISTICAL ANALYSIS

The diagnostic performance of DSCT coronary angiography for the detection of significant lesions in coronary arteries with QCA as the standard of reference is presented as sensitivity, specificity, positive predictive value and negative predictive value, and positive and negative likelihood ratios with the corresponding 95% confidence intervals (CIs). Comparison between DSCT coronary angiography and QCA was performed on 3 levels: segment-by-segment, vessel-by-vessel (no or any significant stenosis per vessel), and patient-by-patient (no or any significant stenosis per patient). An additional sensitivity analysis to detect significant stenoses was performed after random selection of a single segment per patient to explore the effect of nesting. Inter- and intraobserver variability for the detection of significant coronary artery ste-

nosis was calculated using κ statistics. To determine the intraobserver variability, one observer evaluated 30 (33%, 30 of 100) CT datasets twice with a time interval of 3 weeks.

RESULTS

Patient demographics are shown in Table 1. The mean interval between conventional and DSCT coronary angiography was 4.0 ± 4.8 days (range 0 to 17 days). All scans were performed without the use of oral or intravenous beta-blockers. Mean scan range was 11.9 ± 1.1 cm (range 9.3 to 13.8 cm). Mean CT acquisition time was 8.6 ± 1.5 s (range 5.7 to 12.7 s). Pitch varied between 0.20 and 0.53. Mean heart rate was 68 ± 11 beats/min (range 44 to 107 beats/min). The overall radiation exposure for CT coronary angiography was estimated as 11.1 to 14.4 (men to women) mSv; 71 (71%, 71 of 100) patients had long-term beta-blocker medication. The estimated radiation exposure of DSCT coronary angiography was 13.5 to 16.9 mSv (men to women) in low heart rates (mean 56 beats/min), 10.7 to 13.8 mSv (men to women) in moderate heart rates (mean 68 beats/min), and 8.3 to 9.6 mSv (men to women) in high heart rates (mean 81 beats/min). In 5% (5 of 100) of patients with a ventricular extrasystole and in 3% (3 of 100) of patients with a premature atrial complex, ECG editing was successful. A single dataset for the assessment of significant stenoses was used in 81%, 2 datasets in 16%, and 3 datasets in 3% of patients in order to obtain optimal image quality on a per-segment level.

Table 1. Patient Demographics (n = 100).

Age, yrs (range)	**61 ± 11 (28–87)**
Men, %	79
Women, %	21
Clinical presentation	
Atypical angina, %	18
Typical angina, %	55
Unstable CAD, %	27
Risk factors	
Hypertension, %	58
Hypercholesterolemia, %	55
Smoker, %	63
Diabetic mellitus, %	19
Family history of CAD, %	38
Obese (body mass index ≥30 kg/m^2), %	65
Invasive coronary angiography	
Absence of CAD, %	16
Nonsignificant disease, %	7
Single-vessel disease, %	31
Multivessel disease, %	46

CAD = coronary artery disease; Unstable CAD = patients with unstable angina or non–ST-segment elevation myocardial infarction.

Image quality was classified as good in 94% (1,400 of 1,489) and poor in 6% (89 of 1,489) on a per-segment level. Reasons for poor image quality were breathing motion artifacts (33%, 29 of 89), cardiac motion artifacts (14%, 12 of 89), severe calcifications (46%, 41 of 89), or low contrast-to-noise (8%, 7 of 89).

DIAGNOSTIC PERFORMANCE OF DSCT CORONARY ANGIOGRAPHY

The diagnostic accuracy of DSCT to detect significant stenoses on a patient-, segment-, and vessel-based analysis is detailed in Table 2. Typical examples are shown in Figure 1 and Figure 2.

PATIENT-BY-PATIENT ANALYSIS

Twenty patients with either an angiographically normal coronary angiogram (n = 16) or with nonsignificant disease (n = 4) were correctly identified with DSCT. Three patients were incorrectly classified as having single-vessel disease. One patient with significant disease was incorrectly classified as having nonsignificant disease with DSCT. Agreement between DSCT coronary angiography and QCA on a per-patient (no or any disease) level was good (κ value 0.89). Agreement between both techniques for classifying patients as having no, single-, or multivessel disease was very good (κ value 0.85).

VESSEL-BY-VESSEL ANALYSIS

One significantly diseased left anterior descending artery and 2 significantly diseased right coronary arteries were incorrectly classified as nonsignificantly diseased on the CT scan. Sensitivity for the detection of significantly diseased left anterior descending coronary arteries was 98%, for the right coronary arteries 96%, and for the left main and circumflex coronary arteries 100%. Agreement between CT coronary angiography and QCA on a per-vessel level was very good (κ value 0.85).

SEGMENT-BY-SEGMENT ANALYSIS

A total of 1.489 segments that were visualized with invasive coronary angiography were analyzed with DSCT coronary angiography. There were 12 (5.5%, 12 of 220) segments, which were incorrectly classified as having nonsignificant stenosis by DSCT, of which 3 segments demonstrated poor image quality due to cardiac motion artifacts in 2 segments (mean heart rates 65 and 78 beats/min) and due to severe calcifications in 1 segment. There were 69 (5.4%, 69 of 1,269) segments, which were incorrectly classified as having a significant stenosis by DSCT, of which 19 segments demonstrated poor image quality due to severe calcifications in 16 segments, a cardiac motion artifact in 1 segment (mean heart rate 68 beats/min), a breathing artifact in 1 segment, and low contrast-to-noise in 1 segment.

Agreement between CT coronary angiography and QCA on a per-segment level was very good (κ value 0.81). The κ value of inter- and intraobserver variability for the detection of a significant stenosis per segment was 0.83 and 0.85, respectively.

Table 2. Diagnostic Performance and Predictive Value of DSCT Coronary Angiography for the Detection of Significant (≥50%) Stenoses.

	Prevalence of Disease (%)	n	TP	TN	FP	FN	κ	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	ACC (%)	+LR	−LR
Patient-based analysis														
All patients	77	100	76	20	3	1	0.88	99 (92–100)	87 (65–97)	96 (89–99)	95 (74–100)	96 (92–100)	7.6	0.01
Segment-based analysis														
All segments	15	1,489	208	1,200	69	12	0.81	95 (90–97)	95 (93–96)	75 (69–80)	99 (98–99)	95 (93–96)	17.4	0.06
Proximal segments	13	449	53	368	25	3	0.76	95 (84–97)	94 (91–96)	68 (56–78)	99 (97–100)	94 (92–96)	14.9	0.06
Midsegments	26	289	71	192	23	3	0.79	96 (88–99)	89 (84–93)	76 (65–84)	98 (95–100)	91 (88–94)	9	0.05
Distal segments	13	305	37	258	7	3	0.86	93 (79–93)	97 (94–99)	84 (69–93)	99 (96–100)	97 (95–99)	35.0	0.08
Side branches	11	446	47	382	14	3	0.83	94 (82–98)	97 (94–98)	77 (64–87)	99 (98–100)	96 (94–98)	26.6	0.06
Vessel-based analysis														
All vessels	38	400	148	223	26	3	0.85	98 (96–99)	90 (85–93)	85 (79–90)	99 (96–100)	93 (90–95)	9.4	0.02
LM	7	100	7	92	1	0	0.93	100 (100)	99 (93–100)	88 (47–99)	100 (95–100)	99 (97–100)	93	0
LAD	51	100	50	35	14	1	0.70	98 (95–100)	71 (57–83)	78 (66–87)	97 (84–100)	85 (78–91)	3.4	0.03
CX	47	100	47	46	7	0	0.86	100 (100)	87 (74–94)	87 (74–94)	100 (90–100)	93 (88–98)	7.6	0
RCA	46	100	44	50	4	2	0.88	96 (92–100)	93 (81–98)	92 (79–97)	96 (86–99)	94 (89–99)	12.9	0.05

According to the 17-segment modified American Heart Association classification, 1,489 segments and 400 vessels visualized with conventional angiogram were included for segment and vessel analysis, respectively. For patient-based analysis, 100 patients were included. Values in parentheses represent upper and lower bound for 95% confidence interval. ACC = accuracy; CX = circumflex coronary artery; DSCT = dual-source computed tomography scanner; FN = false negative; FP = false positive; LAD = left anterior descending coronary artery; LM = left main coronary artery; NPV = negative predictive value; PPV = positive predictive value; RCA = right coronary artery; TN = true negative; TP = true positive; +LR = positive likelihood ratio; −LR = negative likelihood ratio.

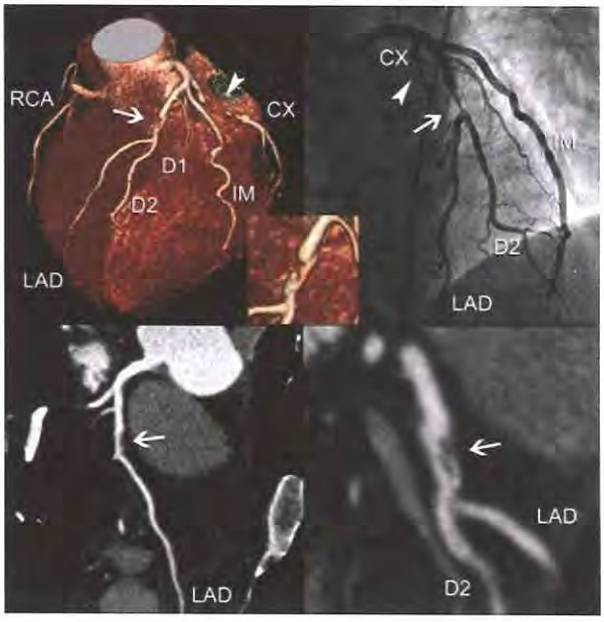

Figure 1. A Significant Lesion in the LAD.

Volume-rendered dual source computed tomography scanner image (colored image) and corresponding conventional angiography image of the right coronary artery (RCA), left anterior descending artery (LAD), circumflex artery (CX), intermediate branch (IM), diagonal branches (D1, D2) in a 57-year-old man with stable angina and equivocal bicycle test. Mean heart rate during scanning was 78 beats/min. A significant lesion was found in the midpart of the LAD (arrow) with detailed color inlay, curved multiplanar reconstruction (bottom left), and maximum intensity projections image (bottom right). The proximal part of the CX showed an occlusion (arrowhead).

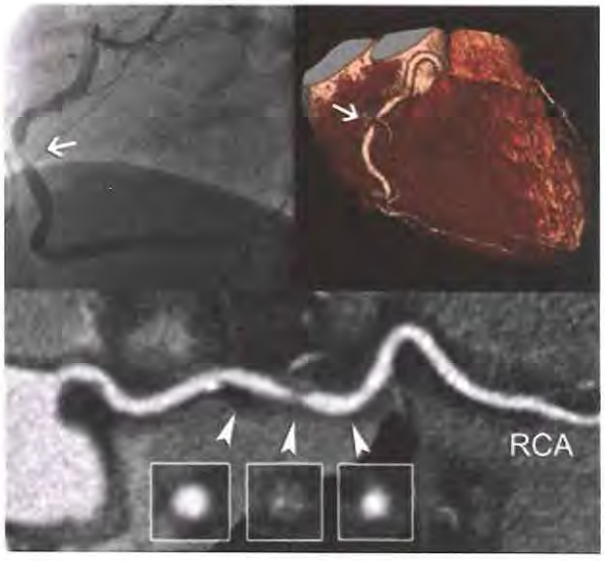

Figure 2. A high-grade stenosis in the midpart of the RCA.

Conventional angiography image and corresponding volume-rendered dual source computed tomography scanner image (colored image) in a 68-year-old man presenting with unstable coronary artery disease. Mean heart rate during scanning was 66 beats/min. The arrow indicates a high-grade stenosis in the midpart of the right coronary artery (RCA). The arrowheads in the curved multiplanar reconstruction image (bottom) indicate cross sections proximal, within, and distal from the occlusion (arrowheads).

Table 3 shows the diagnostic accuracy of DSCT to detect significant coronary stenoses in patients with low (17 ± 27), intermediate (198 ± 96), and high (927 ± 727) Agatston calcium scores based on per-segment–based analysis.

Table 3. Influence of Agatston Score on Diagnostic Accuracy of DSCT Coronary Angiography (a Segment-Based Analysis).

Group	Mean Agatston Score	Prevalence of Disease (%)	n (Segments)	TP	TN	FP	FN	κ	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	ACC (%)	+LR	−LR
1	17 ± 27	8	520	39	471	6	4	0.88	91 (77–97)	99 (97–99)	86 (73–94)	99 (98–100)	98 (97–99)	72.4	0.10
2	198 ± 96	17	477	76	376	20	5	0.83	94 (86–98)	95 (92–97)	79 (69–87)	99 (97–100)	95 (93–97)	18.7	0.07
3	927 ± 727	20	492	93	353	43	3	0.74	97 (90–99)	89 (86–92)	68 (60–76)	99 (97–100)	91 (88–93)	8.9	0.04

Values in parentheses represent upper and lower bound for 95% confidence interval. Abbreviations as in Table 2.

Table 4. Influence of Heart Rate on the Diagnostic Accuracy of DSCT Coronary Angiography (a Segment-Based Analysis).

Mean Heart Rate (s)	N (Segments)	Prevalence of Disease (%)	TP	TN	FP	FN	κ	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	ACC (%)	+LR	−LR	Eff. Dose (mSv)
56.1 ± 4.2	480	20	93	358	26	3	0.83	97 (90–99)	93 (90–95)	78 (69–85)	99 (97–100)	94 (92–96)	14.3	0.07	13.5–16.9
67.9 ± 3.8	490	12	54	418	15	3	0.83	95 (85–99)	97 (94–98)	79 (66–87)	99 (98–100)	96 (95–98)	27.4	0.05	10.7–13.8
80.7 ± 8.5	519	13	61	424	28	6	0.74	91 (81–96)	94 (91–96)	68 (58–78)	99 (97–99)	93 (91–96)	14.7	0.10	8.3–9.6

Values in parentheses represent upper and lower bound for 95% confidence interval. Eff. Dose = effective dose (men–women); other abbreviations as in Table 2.

Table 5. Diagnostic Performance and Predictive Value of DSCT Coronary Angiography for the Detection of Significant (≥50%) Stenoses in Patients With Atypical Angina, Typical Angina, or Unstable CAD.

	Prevalence of Disease (%)	N	TP	TN	FP	FN	κ	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	ACC (%)	+LR	−LR
Patient-based analysis														
Atypical angina	39	18	7	11	0	0	1.00	100 (56–100)	100 (68–100)	100 (56–100)	100 (68–100)	100	—	0
Typical angina	89	55	49	4	2	0	0.78	100 (91–100)	67 (24–94)	96 (85–99)	100	100 (91–100)	3	0
Unstable CAD	78	27	20	5	1	1	0.79	95 (74–100)	100 (52–100)	100 (40–100)	86 (73–99)	96 (83–100)	—	0.05
Segment-based analysis														
Atypical angina	6	281	17	260	4	0	0.89	100 (77–100)	99 (96–100)	81 (57–94)	100 (98–100)	99 (97–100)	66.0	0
Typical angina	17	809	125	633	42	9	0.79	93 (87–97)	94 (92–95)	75 (67–81)	99 (97–99)	94 (92–95)	15.0	0.07
Unstable CAD	17	399	66	307	23	3	0.80	96 (87–99)	93 (90–95)	74 (64–83)	99 (97–99)	93 (91–96)	13.7	0.05

Abbreviations as in Table 1 and Table 2.

Patients were divided into 3 groups based on the mean heart rate during DSCT. There was no significant difference in diagnostic accuracy on a segment-based analysis between these groups (Table 4).

In patients with low heart rates (mean 56.1 beats/min), optimal datasets reconstructed during the mid- to end-diastolic phase were selected in 94% (31 of 33) of patients, and additional datasets during the end-systolic phase were needed in 6% (2 of 33) of patients. In patients with intermediate heart rates (mean 67.9 beats/min), optimal datasets reconstructed during the mid- to end-diastolic phase were selected in 74% (25 of 34) of patients, and additional datasets in the end-systolic phase were needed in 26% (9 of 34) of patients. In patients with high heart rates (mean 80.7 beats/min), optimal datasets reconstructed during the end-systolic phase were selected in 91% (30 of 33) of patients, and additional datasets in the mid- to end-diastolic phase were needed in 9% (3 of 33) of patients. Table 5 demonstrates the diagnostic accuracy of DSCT to detect significant coronary stenoses in patients with atypical and typical angina, and unstable coronary artery disease based on a segment-based analysis.

A sensitivity analysis was performed after random selection of a single segment per patient. The sensitivity was calculated as 92%

(12 of 13, 95% CI 87 to 96); specificity was 94% (82 of 87, 95% CI 90 to 99); positive predictive value was 71% (12 of 17, 95% CI 62 to 80); and negative predictive value was 99% (82 of 83, 95% CI 97 to 100).

DISCUSSION

Earlier studies using 4- and 16-slice CT scanners reported moderate-to-good diagnostic accuracy to detect significant lesions (1-8) (14), but the technique was seriously limited by the presence of unevaluable segments that were, on average, 22% and 9% for the 4- and 16-slice CT, respectively (14). In a recent multicenter study using 16-slice CT scanners, the percentage of unevaluable coronary segments was 29% (4).

The development of 64-slice CT scanners involved a significant improvement in image quality and robustness of CT coronary angiography; however, on average, 5% and in one report even 12% of segments were reported to be unevaluable, and diagnostic accuracy was reduced at higher heart rates (9, 10, 17, and 18).

The introduction of DSCT is another step forward. This scanner is equipped with 2 X-ray tubes (dual source) thereby significantly reducing the temporal resolution to 83 ms independent of heart rate, using single-segment reconstruction. In non-DSCT systems, multisegment algorithms are used to improve temporal resolution. However, this approach is very dependent on a regular heart rate. Minor variation in the time interval between consecutive heart beats can result in interpolation artifacts and image blurring. Furthermore, multisegment reconstruction algorithms require a lower pitch thus longer scan times, more contrast material, and a higher radiation exposure. Multisegment approaches can also be applied in DSCT, resulting in a mean temporal resolution of up to 40 to 60 ms at 0.33 s gantry rotation time. This approach is not recommended for coronary angiography examinations, but may be useful for advanced functional evaluation (15).

With the DSCT scanner we were able to evaluate all coronary segments irrespective of heart rate and image quality. Despite the use of the high-speed DSCT scanner, poor image quality due to cardiac motion artifacts was observed in 14% of the coronary segments. However, the incidence of poor image quality occurred independent of heart rate, and good image quality could also be obtained in high heart rates.

We demonstrated that DSCT coronary angiography had a high diagnostic accuracy to detect significant coronary lesions on a per-segment-based level as compared with QCA. We selected a $\geq$50% diameter stenosis as the cutoff criterion for significant coronary artery disease to allow comparison with the majority of previous published reports (19). A segmental analysis is clinically useful in patients referred for coronary angiography to assess location (proximal, mid, distal, right coronary artery, left anterior descending artery, circumflex artery); severity (luminal

narrowing ≥50%); and extent (1-, 2-, or 3-vessel disease) of coronary artery disease, which determines the value of CT scanning as an alternative to invasive coronary angiography. The patient-based diagnostic accuracy was high (96%), and a negative DSCT scan reliably ruled out the presence of a significant coronary stenosis in patients with atypical and typical angina, and unstable coronary artery disease (Table 5). These findings indicate that DSCT scanning is reliable as a gatekeeper of invasive coronary angiography.

In patients with a positive CT scan showing a severe (>70% diameter stenosis) lesion or a totally occluded vessel, no further evaluation is necessary. However, a positive CT scan with an estimated lesion severity of around 50% has limited value since it poorly discriminates functionally significant lesions from the ones that are not hemodynamically important (20). In this situation an additional functional imaging test such as myocardial perfusion scintigraphy or stress echocardiography would be a logical step before referring the patient for an invasive angiogram and possible revascularization. In patients deemed necessary to undergo revascularization, direct referral to the cathlab may be more logical with invasive assessment of the functional relevance of a lesion using fractional flow reserve and performance of percutaneous coronary intervention in the same session.

Lastly, new developments in CT coronary angiography are desirable for further improvement in clinical performance. Increased gantry rotation speed can further improve temporal resolution, but structural modifications will be required to account for a substantial increase in mechanical forces on the gantry. An alternative concept is the use of multiple (>2) X-ray sources and detectors within a single gantry, thereby obviating the need for an increased gantry rotation speed to improve temporal resolution. Further improved spatial resolution of less than 0.6 mm can be achieved by the use of smaller detector rows. However, an equal contrast-to-noise ratio requires an exponential increase in X-ray power, which will result in an excessive X-ray radiation exposure. Thus, new detector technology is needed to further improve spatial resolution.

LIMITATIONS

Dual source computed tomography scanner coronary angiography should not be performed in patients with significant renal dysfunction or contrast intolerance. This further restricts the use of CT coronary angiography to selected patients, which should be taken into account when the technique is going to be applied in general clinical practice.

One advantage of DSCT is that patients with higher heart rates do not require premedication with beta-blockers because necessary treatment with beta-blockers before CT scanning hampers the CT throughput. The majority of patients (73%) in our study population already received long-term beta-blocker treatment and, therefore, did not benefit from an increased workflow. However, the use of DSCT in low or intermediate risk patient groups with expected lower use of chronic beta-blockers could be more efficient in terms of diagnostic throughput.

The rather high radiation exposure with CT coronary angiography is of concern. In our study, the overall effective dose for DSCT coronary angiography was estimated as 11.1 to 14.4 mSv (men/women), which is lower than the reported effective dose in 64-slice CT angiography (15.2 to 21.4 mSv men/women) (21). The significant reduction of effective radiation dose (8.3 to 9.6 mSv men/women) in high (>80 beats/min) heart rates as compared with low (<60 beats/min) heart rates (13.5 to 16.9 mSv men/women) can mainly be ascribed to an increased pitch and, therefore, shorter scan times in patients with high heart rates. However, compared with the effective dose in diagnostic coronary angiography (3 to 10 mSv) (22), the effective dose in DSCT coronary angiography still remains relatively high.

In this initial experience with the DSCT scanner, we selected a relatively wide pulsing window (25% to 70% of the R-R interval), which allows for reconstruction of datasets during both the mid- to end-diastolic phase and end-systolic phase to obtain optimal image quality. However, there is a delicate balance between the width of the pulsing window and radiation exposure to the patient. Earlier technical feasibility studies demonstrated a significant reduction of the effective radiation dose by using a smaller width of the pulsing window (15). Further clinical studies should establish which pulsing window provides the optimal balance between radiation exposure and image quality, and the effect of a small pulsing window on diagnostic accuracy.

Persistent arrhythmias preclude accurate assessment with DSCT. For the purpose of this study, we excluded patients with persistent arrhythmias, which was also an exclusion criteria in studies using 64-slice scanners. However, our results demonstrate that DSCT technology enables us to scan patients with minor heart rate irregularities, such as a ventricular extrasystole or a premature atrial complex by automatically switching off ECG pulsing during irregular heartbeats. This enables the operator to perform ECG editing to correct for minor heart rate irregularities.

Severe calcifications remain problematic. Calcifications obscure the underlying lumen and preclude judgment of coronary lumen integrity resulting in overestimation of the severity of a coronary stenosis. This explains the observation that in 84% (16 of 19) of segments, which were incorrectly classified as having a significant stenosis by DSCT, severe calcifications resulted in poor image quality. In patients with high (mean 927 ± 727) Agatston scores, diagnostic accuracy was lower (91%) as compared with patient with low (mean 17 ± 27) Agatston scores (98%) (Table 3).

Our study was performed in a selected population consisting of symptomatic patients who were referred for conventional coronary angiography. This was evidenced by the fact that our study population had a high prevalence of coronary disease (77%, 77 of 100), and that a fairly large population had multivessel disease (46%, 46 of 100). In this population, DSCT coronary angiography performed well to excellent, but it remains to be demonstrated that such a high diagnostic accuracy will be achieved in a symptomatic patient population with a low-to-intermediate prevalence of disease or in a nonchest-pain population.

CONCLUSIONS

Our study was performed in a high-risk population with a wide range of symptoms who were referred for conventional coronary angiography. Dual source computed tomography coronary angiography demonstrated a high diagnostic accuracy for the detection or exclusion of significant stenoses in patients with various heart rates without exclusion of unevaluable segments. These results indicate that the technique may now be tested in a cohort with a low-to-intermediate pretest probability of coronary artery disease or in patients with nonanginal chest pain to establish the role of DSCT coronary angiography in the management of patients with suspected coronary artery disease.

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CHAPTER 3

COMPARISON OF DIAGNOSTIC ACCURACY OF 64-SLICE COMPUTED TOMOGRAPHY CORONARY ANGIOGRAPHY IN WOMEN-VS-MEN WITH ANGINA PECTORIS

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ABSTRACT

We compared the diagnostic accuracy of 64-slice computed tomographic (CT) coronary angiography to detect significant coronary artery disease (CAD) in women and men. The 64-slice CT coronary angiography was performed in 402 symptomatic patients, 123 women and 279 men, with CAD prevalence of 51% and 68%, respectively. Significant CAD, defined as ≥50% coronary stenosis on quantitative coronary angiography, was evaluated on a patient, vessel, and segment level. The sensitivity and negative predictive value to detect significant CAD was very good, both for women and men (100% vs 99%, p = NS; 100% vs 98%, p = NS), whereas diagnostic accuracy (88% vs 96%; p <0.01), specificity (75% vs 90%, p <0.05), and positive predictive value (81% vs 95%, p <0.001) were lower in women. The per-segment analysis demonstrated lower sensitivity in women compared with men (82% vs 93%, p <0.001). The sensitivity in women did not show a difference in proximal and midsegments, but was significantly lower in distal segments (56% vs 85%, p <0.05) and side branches (54% vs 89%, p <0.001). In conclusion, CT coronary angiography reliably rules out the presence of obstructive CAD in both men and women. Specificity and positive predictive value of CT coronary angiography were lower in women. The sensitivity to detect stenosis in small coronary branches was lower in women compared with men.

INTRODUCTION

Computed tomographic coronary angiography (CTCA) is a rapidly evolving coronary imaging technique, and a potential alternative to established noninvasive tests for coronary artery disease (CAD). The diagnostic accuracy of CTCA in women per se has not been investigated, but is extrapolated from reports that were performed in populations largely consisting of men (1-9). Although earlier data suggested a discrepancy between men and women with regard to the diagnostic performance of ischemia-driven tests, recent reports using contemporary exercise electrocardiographic (ECG) testing, stress echocardiography, and gated single-photon emission computed tomography myocardial perfusion imaging refute these earlier conclusions, and state similar diagnostic results for both women and men (10-16). Apart from varying age, disease prevalence and severity, additional anatomic and physiologic differences, including body composition, heart rate, coronary calcium, and coronary diameter size, between men and women may affect the diagnostic performance of CTCA. The purpose of this study was to ascertain the diagnostic accuracy of CTCA in women versus men with chest pain to detect or exclude the presence of obstructive CAD.

METHODS

During a 24-month period 402 patients with acute or stable chest pain symptoms who were referred for conventional coronary angiography (CCA) were included in the study. No patients with a history of percutaneous coronary intervention or coronary artery bypass surgery, impaired renal function (serum creatinine >120 μmol/L), persistent arrhythmias, and known intolerance to iodinated contrast material were included. CCA was performed before or after CTCA and served as the standard of reference. The institutional review board of the Erasmus MC Rotterdam approved the study, and all subjects gave informed consent.

Patients with a heart rate >65 beats/min received additional β blockers (50/100 mg metoprolol) 1 hour before the CT examination. All scans were performed on a 64-slice CT scanner with a gantry rotation time of 330 ms, a temporal resolution of 165 ms, and a spatial resolution of 0.4 mm^3 (Sensation 64; Siemens, Forchheim, Germany). For the coronary calcium score, a low-dose, nonenhanced scan was performed with the following, standardized parameters: 32 $\times$ 2 slices per rotation; individual detector width of 0.6 mm, 330-ms rotation time, 3.8-mm/rotation table feed, 120-kV tube voltage, 150-mAs tube current, with activated prospective x-ray tube modulation. The CTCA scan was performed with identical parameters except for a higher tube current between 850 and 960 mAs without prospective ECG x-ray tube modulation. The radiation exposure was estimated using dedicated software (ImPACT, version 0.99x, St. George's Hospital, Tooting, London, United Kingdom). A 95-ml bolus of iomeprol (Iomeron, 400 mg/ml; Bracco, Milan, Italy) was injected intravenously into an antecubital vein at 5 ml/s. A bolus-tracking technique was used to monitor the arrival of contrast in the coronary arteries. The scan was started once the contrast material in the ascending aorta reached a predefined threshold of +100 Hounsfield units.

Datasets were reconstructed immediately after the scan following a stepwise outline. Images were obtained during a half x-ray tube rotation, resulting in an effective temporal resolution of 165 ms. To acquire optimal motion-free images, images were reconstructed by retrospective ECG gating. Initially, a single dataset was reconstructed during the mid-to-end-diastolic phase (350 ms before the next R wave or at 65% of the R-R interval). In case of insufficient image quality of ≥ 1 coronary segments, additional datasets were reconstructed in the diastolic phase (between 250 and 450 ms before the next R wave or between 60% and 70% of the R-R interval). In case of persistent artifacts related to coronary motion, a second reconstruction approach was carried out. Datasets were reconstructed during the end-systolic phase using an absolute forward or percentage technique (between 250 and 400 ms after the previous R wave or between 25% and 35% of the R-R interval). In 34% of the patients (137 of 402) end-systolic reconstructions were used for image analysis. If necessary, multiple datasets of a single patient were used separately to obtain optimal image quality of all available coronary segments.

All scans were carried out within 1 week before or after CTCA. One experienced cardiologist, who was unaware of the CTCA results, identified and analyzed all coronary segments according to the modified 17-segment American Heart Association classification (18). Regardless of diameter size, all segments were included for comparison with CTCA. Segments were classified as normal (smooth parallel or tapering borders), nonsignificantly stenosed (wall irregularities or <50% narrowed), or significantly stenosed (≥50% narrowed). Stenoses were evaluated in the worst view, and classified as significant if the lumen diameter reduction was >50% as measured by a validated quantitative coronary angiographic algorithm (CAAS, Pie Medical, Maastricht, The Netherlands).

For each patient the total calcium score was measured, and expressed using the Agatston score (17). Two experienced, blinded observers evaluated the CTCA data on an offline workstation (Leonardo, Siemens, Forchheim, Germany). The axial source images, as well as multiplanar or curved reformatted reconstructions and maximum intensity projections, were used to evaluate the CT angiograms and assess the presence of significant segmental stenosis. Segments were scored positive for significant CAD if there was ≥50% diameter reduction of the lumen by visual assessment. Segments distal to an occluded segment were excluded. Interobserver disagreement was resolved by a third reader.

Descriptive statistics were performed for coronary segments, vessels, and patients. The diagnostic performance of CTCA for the detection of significant stenoses in the coronary arteries with quantitative coronary angiography (QCA) as the standard of reference is presented as sensitivity, specificity, positive and negative predictive values. Precision of the diagnostic parameters is presented using a 95% confidence interval (CI). Chi-square tests were performed to show significant differences in diagnostic accuracy. Positive and negative likelihood ratios are given. The likelihood ratio incorporates both the sensitivity and specificity of a test and provides a direct estimate of how much a test result will change the odds of having a disease. Post-test odds can be calculated by multiplying the pretest odds (pretest probability/[1 – pretest probability])

by the positive likelihood ratio (sensitivity/[1 − specificity]) and negative likelihood ratio ([1 − sensitivity]/specificity). Post-test probability can be recalculated by using the following formula: (post-test probability = post-test odds/[1 + post-test odds]).

A subanalysis was performed between the 2 genders. Categorical characteristics are expressed as numbers and percentages, and compared between the 2 groups with the chi-square test. Continuous variables are expressed as mean ± SD and compared with an unpaired 2-sided Student's *t* test when normally distributed. When not normally distributed, continuous variables are expressed as medians (25th to 75th percentile range) and compared using the nonparametric Mann-Whitney test. p-Values <0.05 were considered statistically significant.

An additional sensitivity analysis was done to investigate the effect of nesting, as repeated assessments within the same patient were made that were not independent observations. Inter- and intraobserver variabilities for the detection of significant coronary stenosis were determined by κ statistics.

RESULTS

The analysis comprised 123 women and 279 men (Table 1). On average women were older (62 ± 11 vs 58 ± 11 years, $p<0.01$). Hypertension and diabetes were more frequent in women, with no significant difference for body mass index. There were more active smokers among men. Women had lower disease prevalence (51% vs 68%, $p<0.01$), which was defined as having ≥ 1 significant stenosis. The severity and extent of obstructive CAD was significantly lower in women compared with men ($p<0.05$), with fewer cases of multivessel disease (24% vs 35%, $p<0.05$), and more nonobstructive lesions on CTCA (26% vs 17%, $p<0.05$). There was a nonsignificant trend toward fewer absence of CAD on CTCA in women (23% vs 15%, $p = 0.06$). Furthermore, the calcium score was lower in women (146 [0 to 373] vs 207 [18 to 530], $p<0.05$). During the CT scan, women had a significantly higher heart rate than men: 61 ± 7 vs 58 ± 8 beats/min, $p<0.001$). Additional β blockers before CT scanning were administered to 73% of women (90 of 123) and 70% of men (196 of 279) (p = NS), decreasing the mean heart rate from 69 ± 10 to 61 ± 7 beats/min and from 69 ± 11 to 58 ± 8 beats/min, respectively.

The estimated radiation exposure using prospective x-ray tube modulation for the calcium score in women and men was 1.8 and 1.4 mSv and the estimated radiation exposure for the contrast-enhanced scan without prospective x-ray tube modulation was calculated as 17.0 and 13.4 mSv, which is in line with previous reports (19)

The diagnostic performance of CTCA for detecting significant stenoses on a patient-based analysis is detailed in Table 2. All women (63 of 63) and 99% of men (188 of 190) with significant CAD on CTCA were correctly identified by computed tomography (Figure 1 and Figure 2).

Table 1. Patient Demographics (n = 402)

	Women (N:123)	Men (N:279)	P Value
Age (yrs)	62 ± 11	58 ± 11	<0.01
Calcium score (Agatston score)†	146 (0–373)	207 (18–530)	<0.05
Body mass index (kg/m^2)	26.7 ± 5.0	27.0 ± 3.6	NS
Heart rate (beats/min)	61 ± 7	58 ± 8	<0.001
Prevalence of obstructive coronary artery disease	63 (51%)	190 (68%)	<0.01
Atypical angina pectoris	47 (38%)	99 (35%)	NS
Typical angina pectoris	48 (39%)	107 (38%)	
Unstable angina pectoris	14 (11%)	36 (13%)	
Non–ST–segment elevation myocardial infarction	14 (11%)	37 (13%)	
Hypertension‡	78 (63%)	138 (49%)	<0.05
Hypercholesterolemia§	75 (61%)	161 (58%)	NS
Diabetes mellitus#	23 (19%)	28 (10%)	<0.05
Active smoker	30 (24%)	99 (35%)	<0.05
Previous smoker	9 (7%)	20 (7%)	NS
Body mass index ≥30 kg/m^2	34 (28%)	64 (23%)	NS
Previous myocardial infarction	15 (12%)	27 (10%)	NS
Conventional coronary angiography			
Absence of coronary disease	28 (23%)	42 (15%)	<0.05
Nonsignificant disease	32 (26%)	47 (17%)	
Single-vessel disease	34 (28%)	91 (33%)	
Multivessel disease	29 (24%)	99 (35%)	

Mean ± SD.

† Median and quartiles. Values are numbers (percent), unless otherwise indicated. Categorical variables were tested with chi-square test. Continuous variables were tested with unpaired 2-sided Student's t test. If not normally distributed, continuous variables were compared with the Mann-Whitney test. p Values are significant if <0.05.

‡ Blood pressure ≥140/90 mm Hg or treatment for hypertension.

§ Total cholesterol >180 mg/dl or treatment for hypercholesterolemia.

Treatment with oral antidiabetic medication or insulin.

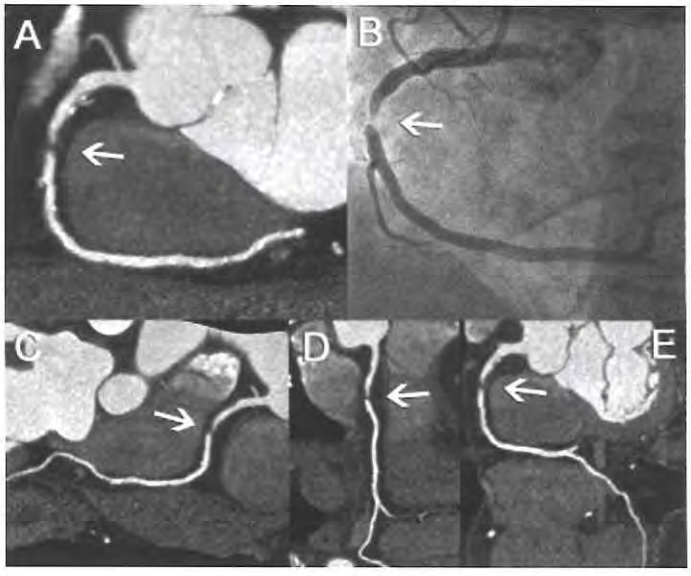

Figure 1. A maximum intensity projected CTCA image (A) depicts the anatomy of the right coronary artery. In the mid right coronary artery, a noncalcified obstructive coronary stenosis is visualized (arrow) with proximally and distally nonobstructive calcified plaques. Three curved multiplanar reconstructed images confirm the significant lesions (arrow) from 3 orthogonal projections (C, D, E), which was confirmed by CTCA (B).

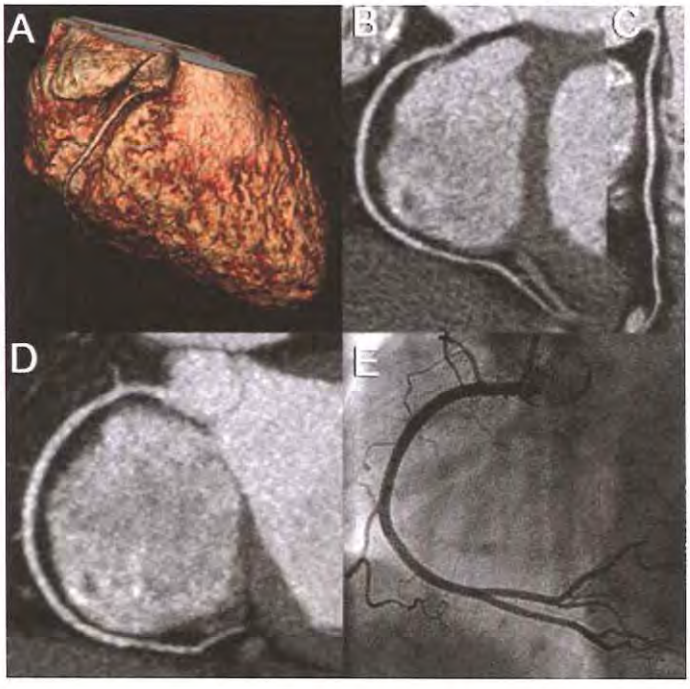

Figure 2. A volume-rendered CTCA image (A) reveals the anatomy of the right coronary artery. Two orthogonal curved multiplanar reconstructed images (B, C) and a maximum intensity projected image (D) disclose a normal coronary artery without obstructive or nonobstructive plaques, which was confirmed by CTCA (E).

Fifteen women (25%, 15 of 60) and 9 men (10%, 9 of 89) with nonsignificant CAD were incorrectly classified as having significant coronary stenoses by CT.

In women, specificity (75% vs 90%, p <0.05), positive predictive value (81% vs 95%, p <0.001), and overall accuracy (88% vs 96%, p <0.01) were significantly lower compared with men (Table 2). Agreement between CTCA and QCA on a per-patient (no or any disease) level for women and men was good (κ value 0.75) and very good (κ value 0.91).

Table 2. Overall Diagnostic Performance of 64-slice Computed Tomographic Coronary Angiography.

	Women (N:123)	Men (N:279)	p Value
Patient level			
Sensitivity	100% (93–100) 63/63	99% (96–100) 188/190	NS
Specificity	75% (62–85) 45/60	90% (81–95) 80/89	<0.05
Positive predictive value	81% (70–88) 63/78	95% (91–98) 188/197	<0.001
Negative predictive value	100% (93–100) 45/45	98% (91–100) 80/82	NS
Diagnostic accuracy	88% (82–94) 108/123	96% (94–98) 268/279	<0.01
+ Likelihood ratio	4.00 (2.58–6.20)	9.78 (4.70–14.25)	—
− Likelihood ratio	0.00 (0-/)	0.01 (0–0.05)	—
Vessel level			
Sensitivity	94% (87–98) 93/99	97% (95–99) 307/315	NS
Specificity	87% (83–90) 342/393	84% (82–87) 676/801	NS
Positive predictive value	65% (56–72) 93/144	71% (66–75) 307/432	NS
Negative predictive value	98% (96–99) 342/348	99% (98–99) 676/684	NS
Diagnostic accuracy	88% (86–91) 435/492	88% (86–90) 983/1,116	NS
+ Likelihood ratio	7.24 (5.58–9.40)	6.25 (5.31–7.34)	—
− Likelihood ratio	0.07 (0.03–0.15)	0.03 (0.02–0.06)	—
Segment level			
Sensitivity	82% (74–88) 111/136	93% (91–96) 400/428	<0.001
Specificity	94% (93–95) 1,551/1,648	92% (91–93) 3,249/3,523	<0.05
Positive predictive value	53% (46–60) 111/208	59% (56–63) 400/674	NS
Negative predictive value	98% (98–99) 1,551/1,576	99% (99–99) 3,249/3,277	<0.05
Diagnostic accuracy	93% (92–94) 1,662/1,784	92% (92–93) 3,523/3,951	NS
+ Likelihood ratio	13.87 (11.25–17.09)	12.02 (10.70–13.50)	—
− Likelihood ratio	0.20 (0.14–0.28)	0.07 (0.05–0.10)	—

Diagnostic performance and predictive value with corresponding likelihood ratios of 64-slice CTCA for the detection of ≥50% stenosis on QCA in women and men. Chi-square test was used for categorical variables. p Values were significant if values <0.05. Values in parentheses represent 95% CIs.

Table 3. Diagnostic Performance of 64-slice Computed Tomography Coronary Angiography Depending on Segment Location.

	Women (N:123)	Men (N:279)	p Value
Analysis of proximal segments			
Sensitivity	96% (84–99) 44/46	98% (93–99) 130/133	NS
Specificity	92% (89-94) 411/446	91% (87–92) 891/983	NS
Positive predictive value	56% (44–67) 44/79	59% (52–65) 130/228	NS
Negative predictive value	100% (98–100) 411//413	100% (99–100) 891/894	NS
Analysis of midsegments			
Sensitivity	93% (81–98) 43/46	96% (90–98) 133/139	NS
Specificity	91% (87–94) 285/314	88% (86–91) 575/650	NS
Positive predictive value	60% (47–71) 43/72	64% (57–70) 133/208	NS
Negative predictive value	99% (97–100) 285/288	99% (98–100) 575/581	NS
Analysis of distal segments			
Sensitivity	56% (31–79) 9/16	85% (74–93) 53/62	<0.05
Specificity	97% (94–98) 364/376	96% (94–97) 754/786	NS
Positive predictive value	43% (23–66) 9/21	62% (51–72) 53/85	NS
Negative predictive value	98% (96–99) 364/371	99% (98–99) 754/763	NS
Analysis of side branches			
Sensitivity	54% (34–72) 15/28	89% (81–94) 84/94	<0.001
Specificity	96% (94–97) 491/512	93% (92–95) 1029/2104	<0.05
Positive predictive value	42% (26–59) 15/36	53% (45–61) 59/84	NS
Negative predictive value	97% (96–99) 491/504	99% (98–100) 1029/1039	<0.05

Chi-square test was used for categorical variables. p Values were significant if values <0.05. Values in parentheses represent 95% CIs.

The diagnostic performance of CTCA for the detection of significant coronary stenosis on a vessel-based analysis is detailed in Table 2. In women, 2 significantly diseased right coronary arteries, 1 left anterior descending coronary artery, and 3 diseased circumflex coronary arteries were incorrectly classified as nonsignificantly diseased. In men, significant coronary stenosis in 2 right coronary arteries, 2 left anterior descending coronary arteries, and 4 circumflex coronary arteries were missed. Significant left main disease was identified in all patients. Fifty-one and 125 nonobstructive vessels were overestimated in women and men and scored as false positives. The diagnostic accuracy was equal in women and men. Agreement between CTCA and QCA on a per-vessel level was both good for women and men (κ value 0.69, 0.74).

After exclusion of anatomically absent segments (833) and segments distal to an occlusion (266), 5,735 of 6,834 potentially available segments (with a maximum of 17 segments per

patient) could be included for comparison with QCA. No segments were excluded for reasons of calcification or poor image quality. The overall sensitivity and specificity of CTCA for the detection of significantly stenosed coronary segments was 91% and 93%. Sensitivity was lower in women (82% vs 93%, $p < 0.001$). Also, the specificity (94% vs 92%, $p < 0.05$) and negative predictive value (98% vs 99%, $p < 0.05$) showed a small, but significant difference between men and women (Table 2).

The performance of CTCA was similar between men and women in the proximal and middle segments (Table 3). However, in the distal segments (56% vs 85%, $p < 0.05$) and side branches, more lesions were not detected in women (sensitivity 54% vs 89%, $p < 0.001$; negative predictive value 97% vs 99%, $p < 0.05$). The specificity (96% vs 93%, $p < 0.05$) was slightly higher in women. Inter- and intraobserver variabilities for detection of a significant stenosis per segment had κ values of 0.70 and 0.72, respectively. Agreement between CTCA and QCA on a per-segment level was good both for women and men (κ value 0.61, 0.68). To exclude the possible confounding effect of nesting, random selection of a single segment per patient was done and the diagnostic accuracy for detecting significant artery disease resulted in a sensitivity 92% (44 of 48; 95% CI 79 to 97), specificity 93% (331 of 356; 95% CI 90 to 95), positive predictive value 64% (44 of 69; 95% CI 51 to 75), negative predictive value 99% (331 of 335; 95% CI 97 to 100).

DISCUSSION

We demonstrated that the sensitivity of 64-slice CTCA to detect significant CAD was almost equally high in women and men (100% vs 99%) due to the very low occurrence of false-negative outcomes. Therefore, the diagnostic accuracy of 64-slice CTCA to rule out the presence of significant obstructive CAD was equally high in women and men and a negative CT scan reliably obviates the need for further downstream evaluation with invasive coronary angiography. The lower prevalence of CAD in women, with a trend toward more nonsignificant CAD ($p = 0.06$) likely contributed to the overestimation of coronary stenosis severity and thus resulted in lower specificity (75% vs 90%).

The segment-based diagnostic accuracy of CTCA performed on a site-by-site analysis (segmental analysis) compared with QCA revealed a more complex outcome. The sensitivity to detect a stenosis was lower in women than in men. The overall reduced sensitivity was mainly caused by the lower sensitivity of CTCA to detect coronary obstructions in distal coronary segments and side branches. This may be partly explained by the combination of a milder stenosis severity and smaller size of the coronary arteries in women than in men. However, this outcome does not affect the reliability to rule out the presence of significant CAD in case of a negative CT scan, because on a segment-based analysis the overwhelming majority of these segments have no significant CAD, and the calculation of the negative predictive value is almost not affected by the higher occurrence of false-negative outcomes.

The studied patients were not a prospective, consecutive group of patients. However, selection was not based on particular patient demographics, but rather on the availability of the 64-slice CT scanner for the examination of cardiac patients.

Fundamental limitations of cardiac computed tomography include the use of radiation, potentially nephrotoxic contrast media, and the need to use β blockers in patients with a fast heart rate. The substantial radiation exposure of 64-slice CTCA for women (17 mSv) and men (13.4 mSv) compared with CCA (3 to 6 mSv) is of concern (19). In this study prospective ECG x-ray tube modulation, which can significantly reduce radiation exposure, was not applied. This technique limits the possibility of reconstructing images in the end-systolic phase. In our study, end-systolic datasets provided better image quality in 34% of patients. Furthermore, the use of prospective ECG x-ray tube modulation requires a regular heart rhythm throughout the scan. In case of an extra-systole, the use of prospective ECG x-ray tube modulation can miss-trigger the x-ray pulse, limiting the possibility to edit valuable reconstruction window datasets during high-dose scanning.

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CHAPTER 4

DIAGNOSTIC ACCURACY OF COMPUTED TOMOGRAPHY ANGIOGRAPHY IN PATIENTS AFTER BYPASS GRAFTING: COMPARISON WITH INVASIVE CORONARY ANGIOGRAPHY

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ABSTRACT

OBJECTIVES: We sought to evaluate the contribution of noninvasive dual-source computed tomography angiography (CTA) in the comprehensive assessment of symptomatic patients after coronary artery bypass grafting (CABG).

BACKGROUND: Assessment of bypass grafts and distal runoffs by invasive coronary angiography is cumbersome and often requires extra procedure time, contrast load, and radiation exposure.

METHODS: Dual-source CTA was performed in 52 (41 men, mean age 66.6 ± 13.2 years) symptomatic post-CABG patients scheduled for invasive coronary angiography. No oral or intravenous beta blockers or sedation were administered before the scan. Mean interval between CABG surgery and CTA was 9.6 ± 7.2 (range 0 to 20) years. Mean heart rate during scanning was 64.5 ± 13.2 (range 48 to 92) beats/min. Seventy-five percent of patients had both arterial and venous grafts. A total of 152 graft segments and 142 distal runoffs vessels were analyzed. Native coronary segments were divided into nongrafted (n = 118) and grafted segments (n = 289). A significant stenosis was defined as ≥ 50% lumen diameter reduction, and quantitative coronary angiography served as reference standard.

RESULTS: The diagnostic accuracy of CTA for the detection or exclusion of significant stenosis in arterial and venous grafts on a segment-by-segment analysis was 100%. Sensitivity, specificity, positive predictive value, and negative predictive value to detect significant stenosis were 95% (95% confidence interval [CI]: 73% to 100%), 100% (95% CI: 96% to 100%), 100% (95% CI: 79% to 100%), 99% (95% CI: 95% to 100%) in distal runoffs respectively; 100% (95% CI: 97% to 100%), 96% (95% CI: 90% to 98%), 97% (95% CI: 93% to 99%), 100% (95% CI: 95% to 100%) in grafted native coronary arteries respectively; and 97% (95% CI: 83% to 100%), 92% (95% CI: 83% to 96%), 83% (95% CI: 67% to 92%), 99% (95% CI: 92% to 100%) in nongrafted native coronary arteries, respectively.

CONCLUSIONS: Noninvasive CTA is successful for evaluating bypass grafts in symptomatic post-CABG patients, whereas invasive coronary angiography is still required for the assessment of significant stenosis in distal runoffs and native coronary arteries.

INTRODUCTION

Recurrent symptoms after surgical revascularization may be caused by progression of disease, either in the native coronary arteries or in the venous or, more rarely, arterial grafts (1). Therefore, comprehensive assessment of symptomatic patients after surgical revascularization should include arterial and venous bypass grafts, distal runoffs, and native coronary arteries. Invasive coronary angiography (ICA) is often rather cumbersome, and the engagement and visualization of venous and arterial bypass grafts frequently prolongs procedure time and is associated with larger contrast use and increased radiation exposure.

Noninvasive computed tomography angiography (CTA) may be useful for reducing the additional invasive procedure time and contrast load if it were proven to be reliable for evaluating bypass grafts and distal runoffs before ICA. Studies using 64-slice computed tomography (CT) scanners reported specificity values of 86% (2) and 76% (3), whereas up to 9% of nongrafted segments and distal runoffs were unevaluable because of presence of severe coronary calcifications, residual coronary motion, or metal clip artefacts. Newer generation CT scanners may improve CT reliability. The dual-source 64-slice CT scanner is equipped with 2 tube-detector systems rotating simultaneously, resulting in an improved temporal resolution of 83 ms (4). Comparative studies demonstrated a high diagnostic performance of dual-source CT coronary angiography to detect significant obstructive coronary artery disease in patients without previous bypass surgery (4–6).

We hypothesized that dual-source CTA allows more accurate detection or exclusion of significant stenoses, in particular, at the graft anastomosis site and smaller distal runoffs. We sought to evaluate whether CTA is complementary to ICA for the evaluation of patients after coronary artery bypass grafting (CABG).

METHODS

Study Population

We studied 58 consecutive symptomatic patients after surgical revascularization that fulfilled the following criteria: sinus heart rhythm, able to breathhold for 15 seconds, and no previous coronary intervention. All patients were scheduled for ICA which was performed within 4 weeks after CTA. Six patients were excluded due to known allergy to Iodinated contrast material (n=1), impaired renal function (serum creatinine> 120 μmol/l) (n=2), atrial fibrillation (n=2) and logistic inability to perform a CT scan (n=1) before ICA. Thus, a total of 52 patients (41 male, mean age 66.6 ± 13.2 years) were included in the study. Our institutional review board approved the study and all patients gave informed consent.

Patient preparation

No oral or intravenous beta-blockers or sedation were administered prior to the scan. All patients received Nitroglycerin (0.4 mg/dose) sublingually just before scanning.

CT Scan Protocol

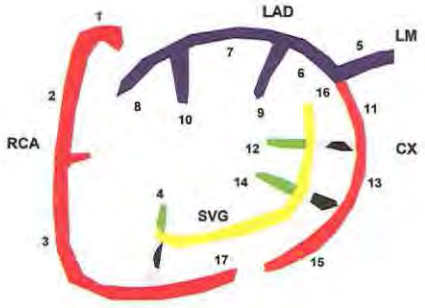
All patients were scanned using a dual-source CT scanner (Somatom Definition, Siemens Healthcare, Forchheim, Germany). The system is equipped with two X-ray tubes and two corresponding detectors mounted on a single gantry with an angular offset of 90°(4). CT angiography scan parameters were: number of X-ray sources 2, detector collimation 32 x 0.6 mm with double sampling by rapid alteration of the focal spot in the longitudinal direction (Z- flying focal spot) (7), rotation time 330 ms, tube voltage 120 kV. The pitch varied between 0.2 for low heart (<40 beats/minute) rates and 0.53 for high heart rates (>100 beats/minute), with individually adapted pitch values for heart rates >40 and <100 beats/minute. Automatic tube current modulation (ref mAs/rotation 380) in x, y, z-direction (Care Dose 4D®, Siemens Healthcare, Forchheim, Germany) and adaptive ECG pulsing (full tube current during 30-65% of the R-R-interval, reduced tube current: 20% of maximum) was applied in all patients.The scan range was extended to the level of the subclavian arteries in patients with internal mammary artery grafts.

A bolus of Iodinated contrast material (Ultravist® 370, Schering AG, Germany), which varied between 80-100 ml depending on the expected scan time, was injected in an antecubital vein followed by a saline chaser (40 ml; flow rate: 4.0-5.0 ml/s). The flow rate (4.0-5.0 ml/s) was adjusted to the scan range (presence of LIMA) and the expected scan time (pitch dependent). A bolus tracking technique was applied to synchronize the data acquisition with the arrival of contrast in the bypass grafts and native coronary arteries.

CT Image Reconstruction and Evaluation

All CT datasets were reconstructed using a single-segment algorithm: slice thickness 0.75 mm; increment 0.4 mm; medium-to-smooth convolution kernel (B26f) and sharp kernel (B46f) resulting in a spatial resolution of 0.6-0.7 mm in-plane and 0.5 mm through-plane (8). Images were reconstructed following a stepwise approach depending on patient's heart rate during scanning as previously described (5).

Two experienced radiologists, blinded to ICA findings, independently scored all CT datasets. In case of a jump graft (two or more anastomoses per arterial or venous graft), the graft was divided into graft segments. All graft segments between the proximal anastomoses and each coronary insertion were evaluated. Distal run-offs and native coronary arteries were evaluated on a per segment level according to the 17-segment modified American Heart Association (AHA) classification (9). The CT image evaluation of distal run-offs and native coronary arteries is illustrated in Figure 1.The distal run-off segments included the segment at which the graft was inserted and all segments located distally to the inserted segment. Native segments were divided into nongrafted and grafted segments. The grafted segments included all segments located proximal to segment at which the graft was inserted.



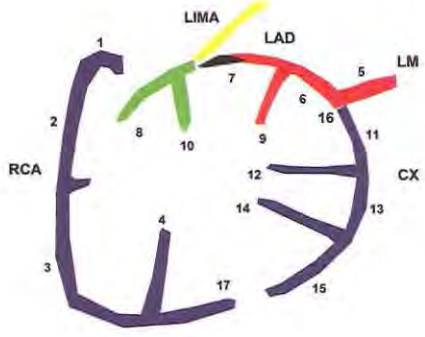


Figure 1A and 1B. Grafts (yellow), distal runoffs (green), native grafted (red), and nongrafted (blue) coronary arteries were evaluated on a per-segment level according to the 17-segment modified American Heart Association classification.
CTA = computed tomography angiography
CX = circumflex artery
LAD = left anterior descending artery
LIMA = left internal mammary artery
LM = left main artery
SVG = saphenous venous graft
RCA = right coronary artery.

Volume rendered images were initially used to visualize the course of the grafts in relation to the coronary arteries. Axial views and (curved) multi-planar reconstructions were used to identify and to classify lesions into significantly (≥50% lumen diameter reduction) diseased or not (<50% lumen diameter reduction). Inter-observer disagreements were resolved in a joint session. One experienced observer evaluated image quality of all graft segments, distal run-off segments and native coronary segments. Image quality was classified as good (defined as absence of any image-degrading artifacts related to motion, noise, vascular clips), moderate (presence of artifacts but evaluation possible with moderate confidence), or poor (presence of image-degrading artifacts and evaluation possible with low confidence).

Quantitative Coronary Angiography (QCA)

One experienced cardiologist, unaware of the results of CTA, identified all graft segments, distal run-off and native coronary segments. Segments were visually classified as normal or luminal irregularities (<20% lumen diameter reduction), or diseased (≥20% lumen diameter reduction). Diseased segments were evaluated using a validated quantitative coronary artery algorithm (QCA) (CAAS®, Pie Medical, Maastricht, the Netherlands). Lesions with ≥50% lumen diameter reduction in two orthogonal planes were considered as significant stenoses. Distal run-off segments supplied by occluded grafts were classified as native grafted segments. All graft and native coronary segments located distally to a total occlusion (100% lumen reduction) and not supplied by collaterals were classified as post-occlusion segments and were excluded from analysis. In addition, native grafted segments with a lumen diameter <1.5 mm were excluded.

Effective Dose

The effective dose (E) for CTA in each patient was estimated by the following equation as proposed by the European Working Group for Guidelines on Quality Criteria in CT:

$$E = EDLP \bullet DLP$$

DLP; dose-length product (cm), EDLP = 0.017 mSv • mGy-1 • cm-1

Statistical analysis

Continuous variables are expressed as means (standard deviation) and categorical characteristics are expressed as numbers and percentages. The diagnostic performance of CTA for the detection of significant stenosis as defined by QCA is presented as sensitivity, specificity, and negative and positive predictive values with the corresponding 95% confidence intervals (CIs), and positive and negative likelihood ratios (LRs) were calculated. Comparison between CTA and QCA was performed on 2 levels: patient-by-patient and segment-by-segment analysis. Interobserver variability for the detection of significant stenosis was determined by κ-statistics.

RESULTS

Patient and scan demographics are summarized in Table 1. The mean BMI was 27.2 ± 5.8 (range 22.0 - 34.5). Forty-seven (90%, 47/52) patients used long-term beta-blockers. The mean interval between CABG surgery and CTA was 9.6 ± 7.2 (range 0-20) years. The mean interval between CTA and ICA was 11.5 ± 14.3 (range 0-14.4) days. Mean scan time was 15.2 ± 4.3 (range 9.2–22.9) seconds. Mean

Table 1. Patient and Scan Demographics (n=52).

Male, n (%)	41 (79)
Age, years	66.6 ± 13.2
Body mass index, kg/m2	27.2 ± 5.8
History	
Family history of CAD, n (%)	21 (40)
Nicotine abuse, n (%)	10 (19)
Hypertension, n (%)	16 (31)
Dislipidaemia, n (%)	31 (60)
Diabetes, n (%)	19 (37)
Previous myocardial infarction, n (%)	22 (42)
Long-term beta-blockers, n (%)	47 (90)
Graft anatomy per patient	
Single graft, n (%)	11 (21)
Two grafts, n (%)	31 (60)
Three grafts, n (%)	9 (17)
More than three grafts, n (%)	1 (2)
Venous and arterial grafts, n (%)	39 (75)
Venous grafts, no arterial grafts, n (%)	6 (12)
Arterial grafts, no venous grafts, n (%)	7 (14)
CT examination	
Heart rate during scanning, beats/min	64.5 ± 13.2
Scan time, sec	15.2 ± 4.3
Pitch	0.26 ± 0.07
Scan length, cm	19.0 ± 5.8
Contrast volume, ml	92.6 ± 17.3
DLP, mGy cm	1726 ± 596
Effective dose, mSv	22.1 ± 2.8

heart rate during scanning was 64.5± 13.2 (range 48-92) beats/minute. The mean effective dose of CTA was 22.1 ± 2.8 mSv.

DIAGNOSTIC PERFORMANCE OF CTA: SEGMENT-BY-SEGMENT BASED ANALYSIS.

The diagnostic performance of CTA for the detection of significant lesions in grafts, distal run-offs and native coronary arteries on a segment-by-segment based analysis is detailed in Table 2. A subanalysis was performed for distal run-offs and native coronary arteries in patients with low (≤65 bpm) and high (>65 bpm) heart rates (Table 3).

GRAFTS

Forty-five (87%, 45/52) patients had venous grafts, and 43 (83%, 43/52) patients had arterial grafts. In one patient, both the right and the left internal mammary artery were used. A total of 63 venous grafts, including 33 jump grafts, representing 102 venous graft segments were evaluated. We observed good image quality in 87% (89/102) of venous graft segments, moderate image quality in 11% (11/102), and poor image quality in 2% (2/102). CTA correctly identified 15/15 occluded venous graft segments and 13/13 significant stenoses (Figure 2). A total of 48 arterial grafts, including 2 jump grafts, representing 50 arterial graft segments were evaluated. We observed good image quality in 90% (45/50) of arterial graft segments, moderate image quality in 8% (4/50), and poor image quality in 2% (1/50). CTA correctly identified 1/1 occluded left internal mammary artery graft. Agreement between CTA and QCA on a per segment level was good (κ-value: 0.99).

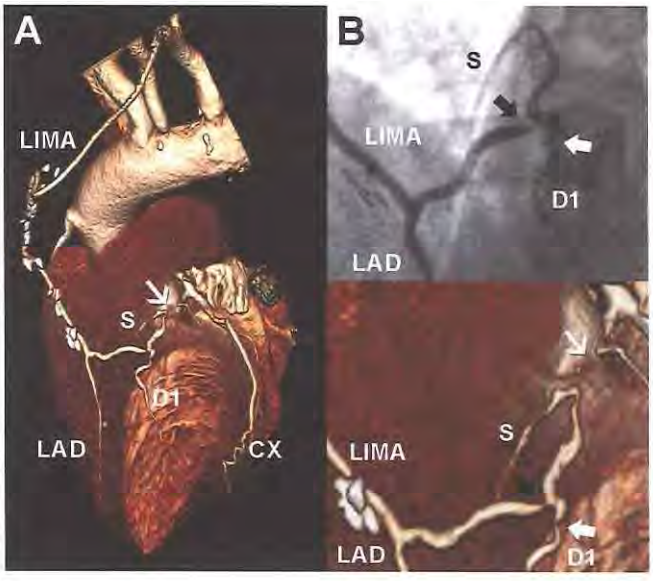


Figure 2. 58-year-old man with progressive chest pain and inconclusive stress test. Volume rendered (VRT) CT image (A) shows an occluded proximal LAD (arrow) and a patent LIMA to the distal left anterior descending artery (LAD) with a jump to first diagonal (D1). A more detailed view (right lower panel) shows a significant stenosis at the anastomosis site of D1 (black arrow) with a second significant stenosis in the proximal D1 run-off (white arrow). There is retrograde filling of a septal branch (S). Corresponding conventional angiogram (B) confirms CT findings.

Table 2. Diagnostic Performance of CTA (segment based analysis).

	Prevalence of disease, (%)	N	TP	TN	FP	FN	κ	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	+LR	-LR
Grafts	19	152	29	123	0	0	0.99	100 (85-100)	100 (96-100)	100 (85-100)	100 (96-100)	-	0
Distal run-offs	13	142	19	122	0	1	0.81	95 (73-100)	100 (96-100)	100 (79-100)	99 (95-100)	-	0.05
Grafted natives	59	289	170	112	5	0	0.79	100 (97-100)	96 (90-98)	97 (93-99)	100 (95-100)	23.4	0
Nongrafted natives	29	118	33	77	7	1	0.85	97 (83-100)	92 (83-96)	83 (67-92)	99 (92-100)	11.7	0.03

+LR indicates positive likelihood ratio; -LR, negative likelihood ratio; N, number; NPV, negative predictive value; PPV, positive predictive value.
Values in parentheses represent upper and lower bound for 95% confidence interval.

Table 3. Diagnostic Performance of CTA; Heart Rate Subanalysis (segment based analysis).

	HR (bpm)	Prevalence of disease, (%)	N	TP	TN	FP	FN	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	+LR	-LR
Distal run-offs	≤65	10	74	7	67	0	0	100 (56-100)	100 (93-100)	100 (56-100)	100 (93-100)	-	0
	>65	19	68	12	55	0	1	92 (62-100)	100 (92-100)	100 (70-100)	98 (89-100)	-	0.08
Grafted natives	≤65	59	135	80	49	4	0	100 (94-100)	93 (81-98)	95 (88-99)	100 (91-100)	13.25	0
	>65	58	154	90	63	1	0	100 (95-100)	98 (91-100)	99 (93-100)	100 (93-100)	64.0	0
Nongrafted natives	≤65	19	43	8	34	1	0	100 (60-100)	97 (83-100)	89 (51-99)	100 (87-100)	35.0	0
	>65	35	75	25	43	6	1	96 (78-100)	88 (75-95)	81 (62-92)	98 (87-100)	7.85	0.04

+LR indicates positive likelihood ratio; -LR, negative likelihood ratio; N, number; NPV, negative predictive value; PPV, positive predictive value. Values in parentheses represent upper and lower bound for 95% confidence interval.

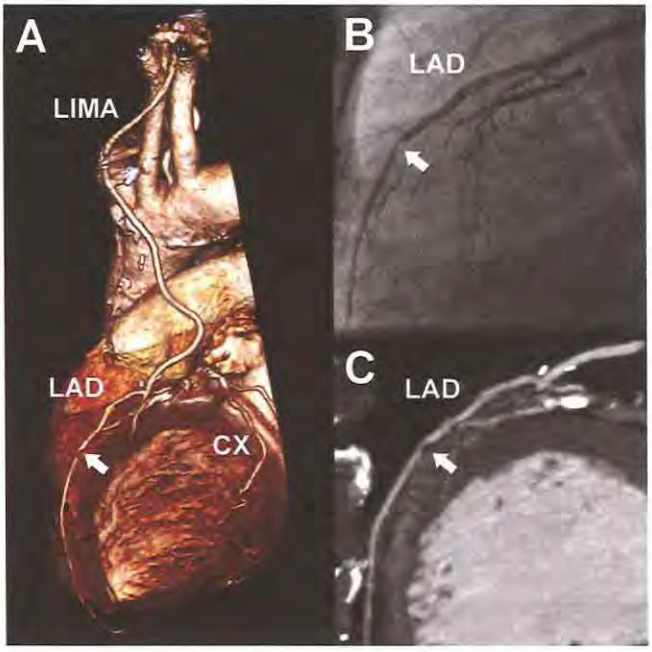


Figure 3. 81-year-old man with stable angina pectoris and a positive treadmill test. VRT image (A) shows a patent LIMA to the distal LAD. The proximal LAD is occluded and a lesion is present in the distal runoff (white arrow). Corresponding cMPR image (B) and conventional angiogram (C) confirm the presence of a significant stenosis (white arrow).

Distal run-offs

ICA identified 136 patent graft segments, supplying a total of 142 distal run-off segments. The image quality was good in 79% (112/142), moderate in 17% (24/142), and poor in 4% (6/142). CTA correctly detected 19/20 significant stenoses (Figure 3) and one significant stenosis was missed in a marginal obtuse. The diagnostic performance of CTA in distal runoffs was lower in patients with heart rate ≥ 65 bpm as compared with heart rate < 65 bpm. Agreement between CTA and QCA on a per segment level was good (κ-value: 0.81).

Native coronary arteries – Grafted

A total of 170 coronary arteries (right coronary artery 67%, 35/52; left main 94%, 49/52; left anterior descending artery 96%, 50/52; left circumflex artery 69%, 36/52) including 289 segments were revascularized by bypass grafting. The image quality was good in 73% (211/289), moderate in 22% (64/289), and poor in 5% (14/289) of segments. CTA detected 170 significant stenoses, including 44 (26%, 44/170) total occlusions (Figure 4) and 5 lesions were overestimated. The diagnostic performance was comparable in both heart rate groups. Agreement between CTA and QCA on a per segment level was good (κ-value: 0.79).

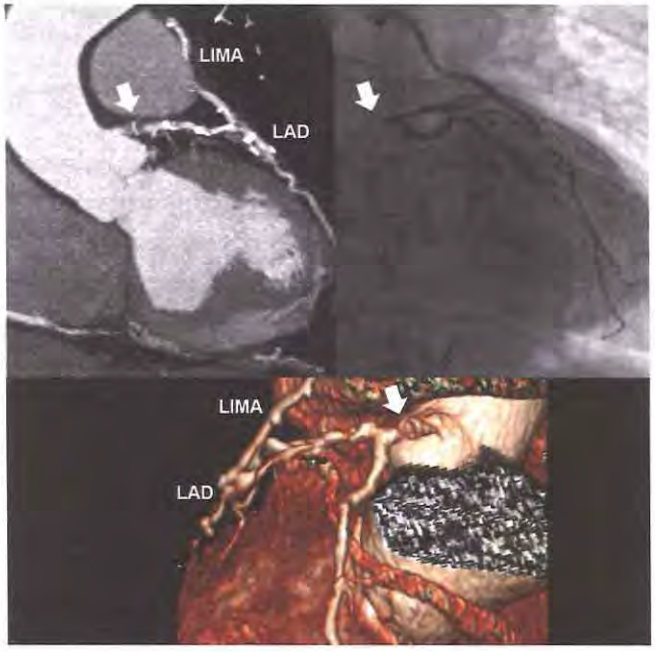


Figure 4. previous myocardial infarction 4 years post CABG. The LIMA and distal run-off vessel were patent. The cMPR (upper right) and VRT (coloured image) demonstrated a total occlusion of the grafted left main (arrow). Corresponding coronary angiogram confirms CT findings (upper left panel).

Native coronary arteries – Nongrafted

A total of 38 coronary arteries including 118 segments were not revascularized by bypass grafting. The image quality was good in 81% (96/118), moderate 16% (19/118), and poor in 3% (3/118). CTA detected 33 significant stenoses, including 9 (27%, 9/33) total occlusions and 7 lesions were overestimated. The diagnostic performance was comparable in both heart rate groups. Agreement between CTA and QCA on a per segment level was good (κ-value: 0.85).

Diagnostic performance of CTA: patient-by-patient based analysis.

We observed a very high prevalence (98%, 51/52) of any significant obstructive disease on a per patient level. The overall diagnostic accuracy of CTA for the detection of any significant stenosis was 100% on a per patient level.

DISCUSSION

The diagnostic work-up of patients with recurrent angina after CABG remains challenging and should include complete assessment of bypass grafts and native coronary arteries.

Non-invasive 64-slice CTA demonstrated a very high diagnostic performance for the detection of obstructive graft disease with sensitivities of 100% for occluded grafts and sensitivities ranging from 80% to 100% for the detection of significant stenosis (2,3,10-15). Only few data are available reporting on the diagnostic performance of CTA for the detection of significant stenosis in the natives. Two studies (2,3) reported a sensitivity of 86% and 89% for the detection of significant stenoses in distal run-offs, and 86% and 97% in nongrafted arteries, respectively. Specificity was 90% and 93% in distal run-offs, and 76% and 86% in nongrafted coronary arteries, respectively. Importantly, 9% to 25% of native segments were unevaluable and overestimation of stenosis frequently occurred.

The 64-slice dual-source CT scanner allows acquisition of images during a shorter time window (83 ms) of the heart cycle resulting in images with less residual coronary motion and more precise delineation of stenoses (8), in particular at the graft distal anastomosis site and smaller distal runoffs. In addition, fast scanning of the whole thorax can be performed in short manageable breath holds (10-15 s) which is, in particular, important in the assessment of arterial grafts.

In our study, we sought to evaluate whether dual-source CTA would permit successful reliable noninvasive evaluation of bypass grafts and distal runoffs to obviate the need for invasive angiographic verification. For this evaluation we performed a segment-by-segment analysis, rather than a per patient analysis, to provide anatomic information about bypass grafts, distal run-offs and native coronary segments. In our evaluation, we included all graft or native coronary segments in the analysis and did not exclude any segment due to motion artifacts or calcifications.

We found a 100% sensitivity on a per segment level for the detection of significant obstructive graft disease and a 95% sensitivity for the detection of significant lesions in distal run-offs. Importantly, the majority of distal anastomosis sites and smaller distal run-offs demonstrated good image quality and could be assessed with high confidence. Furthermore it is noteworthy that on a per patient analysis, all significant obstructive graft disease was correctly identified and no false positives were encountered.

According to the ACCF Appropriate Criteria routine use of 64-slice CT coronary angiography in post-CABG patients has been classified as an inappropriate/uncertain indication (16) or a class IIb indication, level of evidence C (17). Our results indicate that successful reliable noninvasive evaluation of grafts with CTA may obviate the need for invasive angiographic verification and CT angiography can be used for the assessment of graft patency only. If these results are verified in larger, multicenter studies, CTA evaluation of bypass grafts patency may be classified as an appropriate/certain indication. CTA may facilitate planning of subsequent percutanous revas-

cularization by providing accurate anatomical site of graft origin saving considerable procedure time, contrast load and radiation exposure. However, these hypotheses are purely conjectural and require clinical testing. Moreover, ICA is still required to confirm or refute CT evaluation of obstructive disease in distal runoffs and native coronary arteries.

The use of retrospective ECG gating or 'spiral' CT scan mode resulted in a relative high effective dose (22.1 mSv) as compared to diagnostic ICA (8.8 mSv) which is usually higher in the angiographic evaluation of venous and arterial bypass grafts (14). Our rather high patient dose was due to the fact that we began our study with a dual-source prototype scanner. At that time we used a rather wide ECG pulsing window to be able to select optimal motion-free image reconstruction phases. Nowadays patient dose can be significantly reduced by the selection of short windows and the introduction of the possibility to select a very low tube current (4% of maximum tube current; Mindose ®, Siemens Healthcare, Forchheim, Germany) outside the ECG pulsing window, which can reduce effective dose up to 64% (18) (19). Recently, it has been shown that prospective ECG triggering or 'step-and-shoot' CT scan mode can significantly reduce radiation exposure, with reported dose values 1.0-3.0 mSv in patients without previous CABG, but requires a very regular heart rhythm (20) (21).

To put dose concern into perspective, it is important to note that patients after CABG are generally older (± 60 years) and that this is associated with a lower although not negligible life-time attributable risk of cancer incidence or mortality (22).

CONCLUSIONS

We demonstrated that noninvasive dual-source CTA has a very high diagnostic performance to detect or exclude significant stenosis in bypass grafts.

CT angiography should not be considered as a substitute, but rather as complementary to ICA in the diagnostic work-up of symptomatic post CABG patients while ICA is still required to confirm or refute CT evaluation of obstructive native coronary artery disease.

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CHAPTER 5

DUAL-SOURCE CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY FOR DETECTING IN-STENT RESTENOSIS

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ABSTRACT

OBJECTIVE: To evaluate the performance of dual source CT coronary angiography (DSCT-CA) in the detection of in-stent restenosis (≥50% luminal narrowing) in symptomatic patients referred for conventional angiography (CA).

DESIGN/PATIENTS: 100 patients (78 males, age 62 (SD 10)) with chest pain were prospectively evaluated after coronary stenting. DSCT-CA was performed before CA.

SETTING: Many patients undergo coronary artery stenting; availability of a non-invasive modality to detect in-stent restenosis would be desirable.

RESULTS: Average heart rate (HR) was 67 (SD 12) (range 46–106) bpm. There were 178 stented lesions. The interval between stenting and inclusion in the study was 35 (SD 41) (range 3–140) months. 39/100 (39%) patients had angiographically proven restenosis. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of DSCT-CA, calculated in all stents, were 94%, 92%, 77% and 98%, respectively. Diagnostic performance at HR <70 bpm (n=69; mean 58 bpm) was similar to that at HR ≥70 bpm (n=31; mean 78 bpm); diagnostic performance in single stents (n=95) was similar to that in overlapping stents and bifurcations (n=83). In stents ≥3.5 mm (n=78), sensitivity, specificity, PPV, NPV were 100%; in 3 mm stents (n=59), sensitivity and NPV were 100%, specificity 97%, PPV 91%; in stents ≤2.75 mm (n-41), sensitivity was 84%, specificity 64%, PPV 52%, NPV 90%. Nine stents ≤2.75 mm were uninterpretable. Specificity of DSCT-CA in stents ≥3.5 mm was significantly higher than in stents ≤2.75 mm (OR=6.14); 99%CI: 1.52 to 9.79).

CONCLUSION: DSCT-CA performs well in the detection of in-stent restenosis. Although DSCT-CA leads to frequent false positive findings in smaller stents (≤2.75 mm), it reliably rules out in-stent restenosis irrespective of stent size.

INTRODUCTION

Computed tomography angiography is a non-invasive diagnostic tool to visualise coronary arteries (1). The evaluation of stents is, however, hampered by the occurrence of high-density artifacts ("blooming effect") caused by the stent struts. These artifacts cause an apparent enlargement of the stent and preclude appropriate assessment of the in-stent lumen.

In particular, the lumens of small stents, overlapping stents and bifurcation stents are difficult to assess (2). Motion artifacts may further hinder the evaluation of stents (3). Several investigations have evaluated the diagnostic performance of computed tomography in assessing stent patency or the presence of in-stent restenosis (4-16) these studies have included patients with low heart rates and pre-scan preparation with β-blockers.

The introduction of dual source 64-slice computed tomography scanners, with an improved temporal resolution (17) may be helpful to more accurately assess coronary stents.

In this study we evaluated the diagnostic performance of dual source computed tomography coronary angiography (DSCT-CA) for the detection of in-stent restenosis in patients with anginal symptoms after stent implantation.

METHODS

POPULATION

From April 2006 to January 2007, 133 patients with chest pain and prior stent implantation were considered for inclusion in this prospective study. All patients were scheduled for diagnostic conventional angiography. Serum creatinine >120 μmol/l, irregular heart rhythm and known allergy to iodinated contrast agents were exclusion criteria. The recruitment procedure is described in Fig 1. The institutional review board approved the study protocol and all the included patients gave informed consent.

DSCT-CA PROTOCOL

All patients were examined with a dual source CT scanner (Somatom Definition, Siemens, Forchheim, Germany). The scanner design consists of two *x*-ray tubes and two detector arrays mounted at an angle of 90°. Scan parameters were: 120 kV, 330 ms gantry rotation time, 2×32×0.6 mm collimation with z-flying focal spot for both detectors. Using this scan protocol, spatial resolution was 0.4×0.4×0.4 mm (3 17). Pitch values were automatically adapted to the heart rate after an estimation based on the last 10 heartbeats preceding the scan, and varied between 0.20 and 0.43. Current *x*-ray tube modulation was used at full current for 25–70% of the R-R interval. Each tube provided a maximum of 412 mAs/rotation. In patients with heart rates <70 bpm, *x*-ray exposure was (mean (SD)) 15.0 (4.1) mSv in men and 16.7 (5.0) mSv in women; in patients with heart rates ≥70 bpm, *x*-ray exposure was 12.1 (2.6) mSv in men and

13.7 (4.7) in women (values calculated using ImPACT®, version 0.99x, St George's Hospital, Tooting, London, UK).

All patients received sublingual nitroglycerin just before scanning. Contrast agent (Iomeron® 400 mg/ml, Bracco, Italy) was injected into the antecubital vein at a flow rate of 5.0 ml/s, followed by a saline chaser (40 ml). We calculated the contrast volume with the following equation: estimated scan time + scan delay (7 s). The contrast volume varied between 60 and 100 ml depending on the scan time, which in turn varied between 5 and 13 seconds. We used a bolus-tracking technique to synchronize the start of the scan with the arrival of contrast agent in the coronary arteries. A circular region-of-interest (ROI) was positioned in the ascending aorta and the scan was automatically started when a threshold of +100 Hounsfield Units was reached inside the ROI.

Image reconstruction

Given the scanner geometry, a monosegmental algorithm using data from a single heartbeat obtained during a quarter gantry rotation was used for reconstruction. This translated into a temporal resolution equal to one-fourth of the gantry rotation time, that is, 330/4= 83 ms.

First, 0.75 mm-thick images were retrospectively reconstructed during the mid-diastolic to end-diastolic phase. The position of the reconstruction window within the R-R interval varied according to the heart rate (from −400 ms before the R wave for low heart rates to −175 ms for high heart rates). Additional data sets were reconstructed during the end-systolic phase (from +400 ms after the R wave for low heart rates to +200 ms for high heart rates). The reconstruction increment was 0.4 mm. The data set with the fewest motion artifacts was chosen for analysis and reconstructed using a dedicated sharp convolution kernel (B46f, "Heart View").

Quantitative coronary angiography (QCA)

A single observer unaware of the CT results examined the angiograms before contrast injection to identify the sites of stent implantation. The stents were then located within the coronary tree following a 17-segment modified AHA model, as previously described (18 19). Stents and stent edges, the latter defined as 5 mm-long coronary segments proximal and distal to the stents, were evaluated on multiple projections; luminal narrowing ≥50% was classified as significant (restenosis). Validated quantitative coronary angiography software (CAAS II®, Pie Medical, Maastricht, The Netherlands) was used to determine the minimal lumen diameter and derive the per cent diameter stenosis by means of the user-independent method of the interpolated reference diameter, using the angiographic catheter diameter as reference for calibration (20).

DSCT-CA analysis

Two experienced readers evaluated the DSCT-CA studies independently; the readers were unaware of the findings of conventional angiography. In the event of diverging opinions, a consensus was reached and used in the final analysis.

Using axial images, multiplanar reconstructions (MPR) and curved MPR, the stents were visually screened for the presence of in-stent restenosis (≥50% lumen diameter reduction). When multiple stents were implanted contiguously to treat one lesion, they were considered as one single lesion. The assessment of restenosis was based exclusively on the visualization of the in-stent lumen. The presence of distal run-off was not considered as an indicator of patency because retrograde or collateral filling in an occluded stent can also give distal contrast enhancement (Fig 2). All stent edges, defined as 5 mm-long coronary segments proximal and distal to the stents, were also included in the evaluation. In the event of bifurcation stenting, each of the three branches was evaluated. When the stent lumen was uninterpretable (e.g. obscured by high-density artifacts), and in-stent restenosis could not be excluded by DSCT-CA, stents were considered to have restenosis (worst case scenario) (6 7) for the purpose of the analysis.

STATISTICS

The statistical analysis was performed with SPSS, version 12.1 (SPSS Inc., Chicago, Illinois, USA). Results are reported in accordance with the STARD criteria 21. Continuous variables are expressed as mean (standard deviation). Categorical variables are presented as counts and percentages.

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of DSCT-CA for the detection of ≥50% in-stent restenosis, as determined by QCA as reference standard, were computed in two subgroups defined as low heart rate and high heart rate; the definition of the two groups was based on a cut-off heart rate of 70 bpm as previously described by Leber *et al.* (22) and Mollet et al. (19). The low heart rate subgroup comprised patients with heart rates <70 bpm, the high heart rate subgroup comprised patients with heart rates ≥70 bpm.

Sensitivity, specificity, PPV and NPV were then computed in two subgroups defined as *simple configuration* and *complex configuration*: the *simple configuration* subgroup comprised lesions treated with the deployment of one single stent; the *complex configuration* subgroup comprised overlapping stents and bifurcation stenting.

We also computed sensitivity, specificity, PPV and NPV in three subgroups defined by stent diameters, that is, ≥3.5 mm, 3 mm and ≤2.75 mm. When multiple stents were employed to treat one lesion, the diameter of the proximal stent determined the diameter subgroup. This criterion for subclassifying lesions with multiple stents was based on the expectation that small stents were more difficult to evaluate than large stents; we preferred to underestimate the diagnostic performance in the larger stent subgroups rather than overestimating the diagnostic performance in the smaller stent subgroup.

Sensitivity, specificity, PPV and NPV were also computed separately for the right coronary artery (RCA), left main (LM) stem, left anterior descending (LAD) and left circumflex (LCx) arteries. Because the accuracy of DSCT-CA to detect occluded stents might be greater than the accuracy to detect restenosis, we performed separate analyses after excluding totally occluded

segments. Diagnostic test results are presented with corresponding 95% confidence intervals based on binomial probabilities. The χ^2 test was used to compare the frequency of occurrence of restenosis in the different subgroups. The Mann–Whitney U test was used to compare the mean stent diameters in the *heart rate* subgroups and in the *configuration* subgroups.

We determined the effect of heart rate, stent configuration and stent diameter on sensitivity, specificity, PPV, and NPV using logistic regression analysis including patient identification to correct for possible correlation within the individuals who had multiple stents (23). To compensate for multiple testing, we used a significance level of 0.01 and computed 99% confidence intervals (CI).

Interobserver and intraobserver agreement for the detection of re-stenosis were determined by κ-statistics.

RESULTS

BASELINE CHARACTERISTICS AND ANGIOGRAPHIC FINDINGS

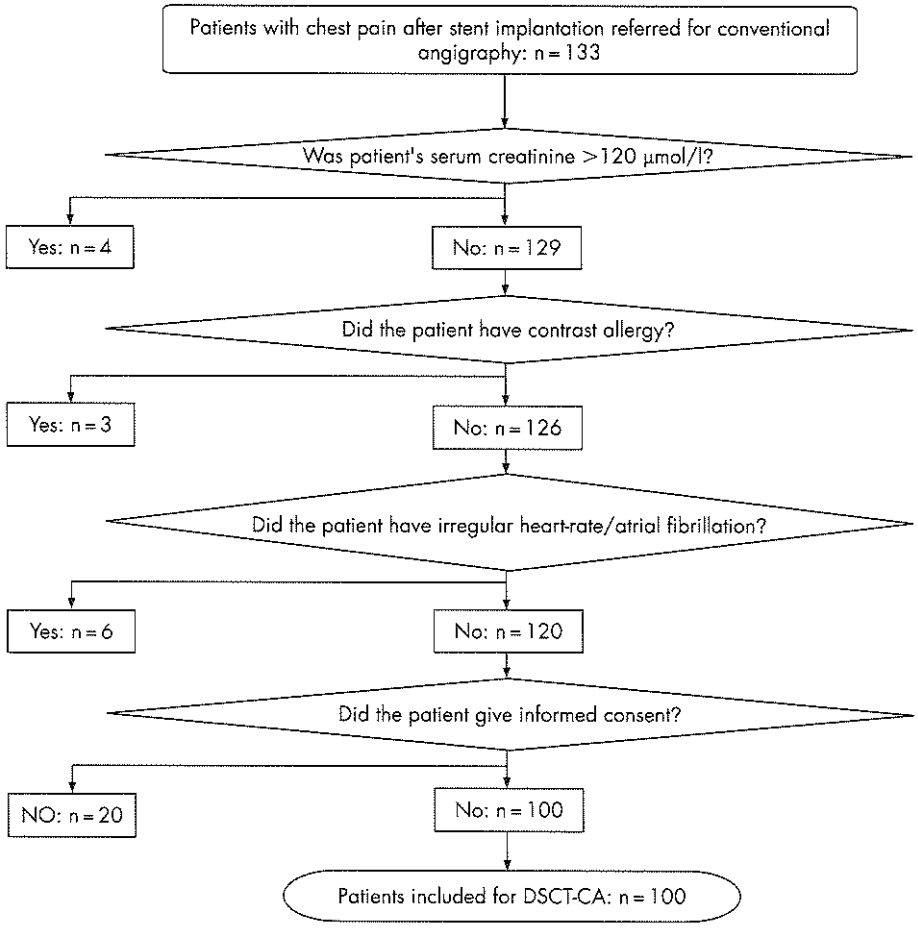
Of the 133 patients screened for inclusion in our study, 33 were excluded because of serum creatinine level >120 μmol/l (n=4), known contrast allergy (n=3), irregular heart rate (n=6) and refusal to undergo DSCT-CA (n=20), so that 100 patients underwent DSCT-CA (Fig 1).

DSCT-CA and conventional angiography were performed 35 (SD 41) months after stenting (range 3–140 months). Seventy patients were on treatment with β-blockers; none of the patients received additional β-blockers before the scan.

The average heart rate during the scan was 67 (SD 12) (range 42–106) bpm. Sixty-nine patients had heart rates <70 bpm and were included in the *low heart rate* subgroup (the average heart rate in this subgroup was 58 (SD 6) (range 42–69) bpm); 31 patients had heart rates ≥70 bpm and were included in the *high heart rate* subgroup (the average heart rate in this subgroup was 78 (SD 9) (range 70–106) bpm).

We examined 178 stented lesions (247 stents used, 1.4 (SD 0.8) stents per lesion); 95 lesions consisted of single stents (*simple configuration* subgroup); the remaining 83 lesions consisted of overlapping stents (n=62) and bifurcations (n=21) (*complex configuration* subgroup). All but one *complex* lesion consisted of stents of the same type. One *complex* lesion was a stent-in-stent implantation consisting of two partially overlapped BX Velocity stents plus three Taxus stents implanted 1 year later (Fig 2); this lesion was classified as a bare metal stent (BMS) lesion. BMS accounted for 37% (65/178) of the stented lesions, drug-eluting stents (DES) accounted for 63% (113/178) of the stented lesions. Restenosis was diagnosed angiographically in 39/178 (22%) stented lesions in 39/100 (39%) patients. Restenosis was found in 27/65 (42%) BMS and in 12/113 (11%) DES. Table 1 summarizes patient baseline characteristics, main angiographic findings and stent types.

Figure 1. Inclusion procedure for the study (from April 2006 to January 2007).



The frequency of in-stent restenosis was 23% (29/124) in the *low heart rate* subgroup and 19% (10/54) in the *high heart rate* subgroup. In the *simple* and *complex configuration* subgroups, frequencies were 18% (17/95) and 26% (22/83), respectively. In the ≥3.5 mm, 3 mm and ≤2.75 mm subgroups, frequencies of restenosis were 19% (15/78), 20% (12/59) and 31% (13/41), respectively. All p values were not significant ($p > 0.05$).

The mean stent diameter in the entire sample was 3.15 (SD 0.58). The mean stent diameters in the *simple* and *complex configuration* subgroups were 3.16 (SD 0.60) mm and 3.15 (SD 0.61) mm, respectively. The mean stent diameters in the *low* and *high heart rate* subgroups were 3.17 (SD 0.61) mm and 3.15 (SD 0.66) mm, respectively. All p values were not significant ($p > 0.05$).

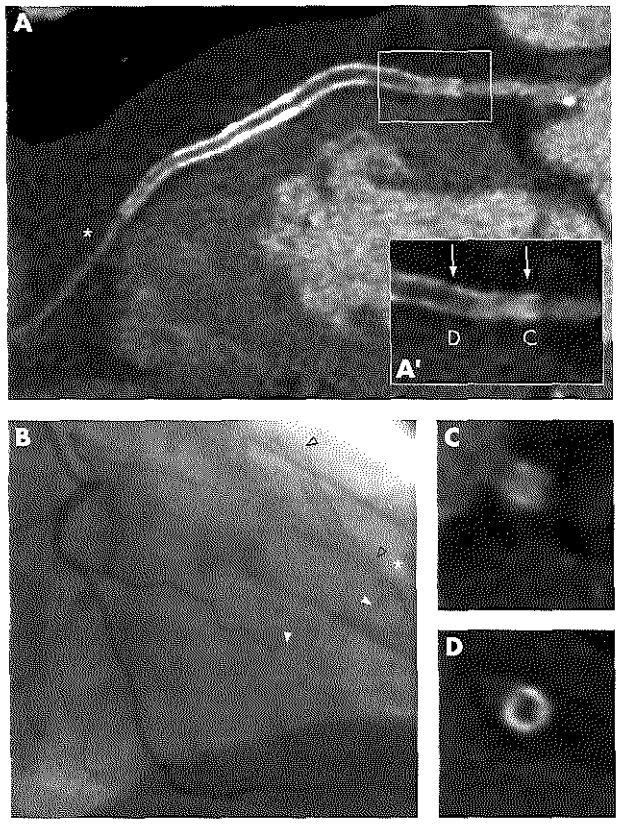


Figure 2. Distal run-off as a criterion of patency. The presence of distal run-off is not always associated with stent patency. (A) A DSCT-CA curved multiplanar reconstruction shows a stented lesion consisting of two BX Velocity stents plus three Taxus stents (stent-in-stent) in the left anterior descending artery (LAD). In spite of the presence of distal run-off (asterisk), in-stent total occlusion is seen. (C–D) Stent cross-sections obtained as indicated in (A') (magnification of (A)) show the appearances of a patent stent (C) and of a totally occluded stent (D), respectively. (B) The corresponding conventional angiogram demonstrates that, distally to the stents (empty arrowheads), the LAD (asterisk) is fed by collateral flow (solid arrowheads). Direct visualization of the stent lumen is therefore mandatory to rule out in-stent restenosis with DSCT-CA.DSCT-CA, dual source coronary computed tomography angiography.

DIAGNOSTIC PERFORMANCE OF DSCT-CA

All 178 stented lesions were detected by DSCT-CA. The stent lumen was judged interpretable in 169/178 (95%) stents. In the remaining nine stents (5%), all of which were ≤2.75 mm in diameter, the lumen was uninterpretable due to high-density artifacts obscuring the in-stent lumen; these stents were scored as having in-stent restenosis. However, these nine small stents were angiographically normal (no in-stent restenosis, DSCT-CA false positives).

Sensitivity, specificity, PPV and NPV in detecting ≥50% restenosis, calculated on all stents, were 94%, 92%, 77% and 98%, respectively. The diagnostic performance of DSCT-CA at heart rates <70 bpm did not differ significantly from that obtained at heart rates ≥70 bpm, as witnessed by widely overlapping confidence intervals. The diagnostic performances obtained in simple stents and overlapping stents/bifurcations were also similar. Likewise, no significant differences were seen between the four major coronary vessels. Table 2 gives sensitivity, specificity, PPV and NPV obtained in the *heart rate* subgroups, in *simple* and *complex configuration* subgroups and in the four major coronary vessels.

Table 1. Baseline Characteristics, Angiographic Findings and Stent Types

Patient number	100
Age (years) (mean (SD))	62 (10)
Men/women	78/22
Cardiovascular risk factors (number)	
Obesity (Body Mass Index ≥30 kg/m²)	23
Smoking	25
Hypertension (≥ 160/95 mm Hg or ongoing treatment)	45
Serum cholesterol >200 mg/dl (5.18 mmol/l)	51
Diabetes mellitus	21
Family history	29
Total number of stents used and types	247
Drug-eluting stents	157
Bare metal stents	90
Frequency of individual diameters and types (number (%))	
2.25	21/247 (9%)
2.5	31/247 (13%)
2.75	17/247 (7%)
3.0	82/247 (33%)
3.5	63/247 (25%)
4.0	20/247 (8%)
4.5	8/247 (3%)
5.0	5/247 (2%)
Taxus	136/247 (55%)
Cypher	21/247 (8%)
BX Velocity	32/247 (14%)
R Evolution	21/247 (8%)
NIR	7/247 (3%)
Multilink	4/247 (1.5%)
Palmaz-Schaz	4/247 (1.5%)
*Other BMS**	22/247 (9%)
Number of lesions and stent types (number (%))†	178
Drug-eluting stents	113 (63%)
Bare metal stents	65 (37%)
Vessel implanted: number (%)	
RCA	60 (34%)
LM stem	11 (6%)
LAD	58 (32%)
LCx	49 (28%)
Patients diagnosed with ≥50% restenosis (number)	39
Lesions with ≥50% restenosis (number (%))	39/178 (22%)
Restenosis	22/39 (56%)
Total occlusion	17/39 (44%)
Stent types with restenosis (number (%))	
Drug-eluting stents	12/113 (11%)
Bare metal stents	27/65 (42%)

*Type not available (implanted before 2003).

†One stent-in-stent implantation consisting of two BX Velocity plus three Taxus stents was classified as BMS; all other complex lesions consisted of stents of the same type.

Table 2. Diagnostic Performance of DSCT-CA in Detecting ≥50% Luminal Narrowing to all Lesions and Subgroup Analysis

	All Lesions	HR<70 Mean=58 (SD 6)	HR≥70 Mean=78 (SD 9)	Simple	Complex	≥3.5 mm	3.0 mm	≤2.75 mm	RCA	LM	LAD	LCx
Total	178	124	54	95	83	78	59	41	60	11	58	49
TP	37	28	9	16	21	15	11	11	8	0	15	14
TN	128	88	40	74	54	63	47	18	48	11	38	31
FP	11 (9)*	7	4	4	7	0	1	10 (9)*	4	0	4	3
FN	2	1	1	1	1	0	0	2	0	0	1	1
Sensitivity	37/39	28/29	9/10	16/17	21/22	15/15	11/11	11/13	8/8	–	15/16	14/15
	0.94 (0.81 to 0.99)	0.96 (0.80 to 0.99)	0.90 (0.54 to 0.99)	0.94 (0.69 to 0.99)	0.95 (0.75 to 0.99)	1 (0.74 to 1)	1 (0.67 to 1)	0.84 (0.53 to 0.97)	1 (0.59 to 1)		0.93 (0.67 to 0.99)	0. (0.66 to 0.99)
Specificity	128/139	88/95	40/44	74/78	54/61	63/63	47/48	18/28	48/52	11/11	38/42	31/34
	0.92 (0.85 to 0.95)	0.92 (0.84 to 0.96)	0.90 (0.77 to 0.97)	0.94 (0.86 to 0.98)	0.88 (0.77 to 0.94)	1 (0.92 to 1)	0.97 (0.79 to 0.99)	0.64 (0.44 to 0.80)	0.92 (0.80 to 0.97)	1 (0.67 to 1)	0.90 (0.76 to 0.99)	0.91 (0.75 to 0.97)
PPV	37/48	28/35	9/13	16/20	21/28	15/15	11/12	11/21	8/12	–	15/19	14/17
	0.77 (0.62 to 0.87)	0.80 (0.62 to 0.90)	0.69 (0.38 to 0.89)	0.80 (0.55 to 0.93)	0.75 (0.54 to 0.88)	1 (0.74 to 1)	0.91 (0.59 to 0.99)	0.52 (0.30 to 0.73)	0.66 (0.35 to 0.88)		0.78 (0.53 to 0.93)	0.82 (0.55 to 0.95)
NPV	128/130	88/89	40/41	74/75	54/55	63/63	47/47	18/20	48/48	11/11	38/39	31/32
	0.98 (0.93 to 0.99)	0.98 (0.93 to 0.99)	0.97 (0.85 to 0.99)	0.98 (0.91 to 0.99)	0.98 (0.89 to 0.99)	1 (0.92 to 1)	1 (0.90 to 1)	0.90 (0.66 to 0.98)	1 (0.90 to 1)	1 (0.67 to 1)	0.97 (0.84 to 0.99)	0.96 (0.82 to 0.99)
After exclusion of totally occluded stents												
Total	161	113	48	87	74	70	55	36	57	11	51	42
TP	20	17	3	8	12	7	7	6	5	0	8	7
TN	128	88	40	74	54	63	47	18	48	11	38	31
FP	11	7	4	4	7	0	1	10	4	0	4	3
FN	2	1	1	1	1	0	0	2	0	0	1	1
Sensitivity	20/22	17/18	3/4	8/9	12/13	7/7	7/7	6/8	5/5	–	8/9	7/8
	0.90 (0.69 to 0.98)	0.94 (0.70 to 0.99)	0.75 (0.21 to 0.98)	0.88 (0.50 to 0.99)	0.92 (0.62 to 0.99)	1 (0.56 to 1)	1 (0.56 to 1)	0.75 (0.35 to 0.95)	1 (0.46 to 1)		0.88 (0.50 to 0.99)	0.87 (0.46 to 0.99)
Specificity	128/139	88/95	40/44	74/78	54/61	63/63	47/48	18/28	48/52	11/11	38/42	31/34
	0.92 (0.85 to 0.95)	0.92 (0.84 to 0.96)	0.90 (0.77 to 0.97)	0.94 (0.86 to 0.98)	0.88 (0.77 to 0.94)	1 (0.92 to 1)	0.97 (0.79 to 0.99)	0.64 (0.44 to 0.80)	0.92 (0.80 to 0.97)	1 (0.67 to 1)	0.90 (0.76 to 0.96)	0.91 (0.75 to 0.97)
PPV	20/31	17/24	3/7	8/12	12/19	7/7	7/8	6/16	5/9	–	8/12	7/10
	0.64 (0.45 to 0.80)	0.70 (0.48 to 0.86)	0.42 (0.11 to 0.79)	0.66 (0.35 to 0.88)	0.63 (0.38 to 0.82)	1 (0.56 to 1)	0.87 (0.46 to 0.99)	0.37 (0.16 to 0.64)	0.55 (0.22 to 0.84)		0.66 (0.35 to 0.88)	0.70 (0.31 to 0.95)
NPV	128/130	88/89	40/41	74/75	54/55	63/63	47/47	18/20	48/48	11/11	38/39	31/32
	0.98 (0.93 to 0.99)	0.98 (0.93 to 0.99)	0.97 (0.85 to 0.99)	0.98 (0.91 to 0.99)	0.98 (0.89 to 0.99)	1 (0.92 to 1)	1 (0.90 to 1)	0.90 (0.66 to 0.98)	1 (0.90 to 1)	1 (0.67 to 1)	0.97 (0.84 to 0.99)	0.96 (0.82 to 0.99)

*Nine stents had uninterpretable lumen; all these were ≤2.75 mm in diameter. These were considered positives for the purpose of the analysis.

Values expressed as means (95% confidence intervals).

FN, false negative; FP, false postive; TN, true negative; TN, true positive.

In the diameter-based subanalysis, we found that NPV was in the range 90–100% in all subgroups. Sensitivity was 100% in ≥3.5 mm stents and in 3 mm stents, but it dropped to 84% in ≤2.75 mm stents. Specificity and PPV were both 100% in the ≥3.5 mm subgroup; the values for specificity and PPV were 97% and 91%, respectively, in the 3 mm subgroup, and 64% and 52%, respectively, in the ≤2.75 mm subgroup. Table 2 gives the diagnostic performance of DSCT-CA in detecting ≥50% luminal narrowing in the different *diameter* subgroups.

In the logistic regression analysis predicting specificity, a stent diameter of ≥3.5 mm had an odds ratio of 6.14 (99%CI 1.52 to 9.79). In predicting the PPV, a stent diameter of ≥3.5 mm had an odds ratio of 3.70 (99%CI 0.98 to 8.90). All other variables were not significant.

The interobserver agreement in detecting restenosis was good (κ-value = 0.78). The intraobserver agreement was very good (κ-value = 0.87).

DISCUSSION

Cardiac catheterisation is the technique of choice for the detection of in-stent restenosis. However, it may involve life-threatening complications and is relatively expensive. The diagnostic accuracy of non-invasive techniques such as exercise testing is known to be suboptimal (24) therefore an alternative non-invasive "gatekeeper" to invasive coronary angiography would be desirable. The reliability of such a technique would have to be demonstrated in various clinical situations (ie, various stent sizes and configurations, higher heart rates) before it could be routinely used in patients with prior coronary artery stenting.

FEASIBILITY OF DSCT-CA AT HIGH HEART RATES

This study showed that DSCT-CA was accurate in detecting in-stent restenosis without the use of pre-scan β-blockers. Although the rate of false positives was slightly higher at high heart rates (PPV=69%) than at low heart rates (PPV=80%), the number of false negatives was low in both subgroups (NPV in the range 97–98%). In addition, the capability to perform DSCT-CA at higher heart rates without the use of β-blockers may be advantageous in terms of reducing radiation exposure. Table speed increases with increasing heart rates in DSCT-CA, which in turn translates into shorter scan times and reduced radiation exposure.

STENT CONFIGURATIONS

To the best of our knowledge, the population evaluated in the present study is the largest available in the literature on coronary CT angiography including overlapping and bifurcation stenting (n=83). Although the differences were not statistically significant, we found that specificity and PPV of DSCT-CA in bifurcation stenting and overlapping stents were slightly lower than those obtained in single stents, probably due to the large amount of metal at the ostium of side branches and at overlapping sites. This excess of metal is a major source of high-density artifacts in CT and may lead to lesion overestimation (Fig 3).

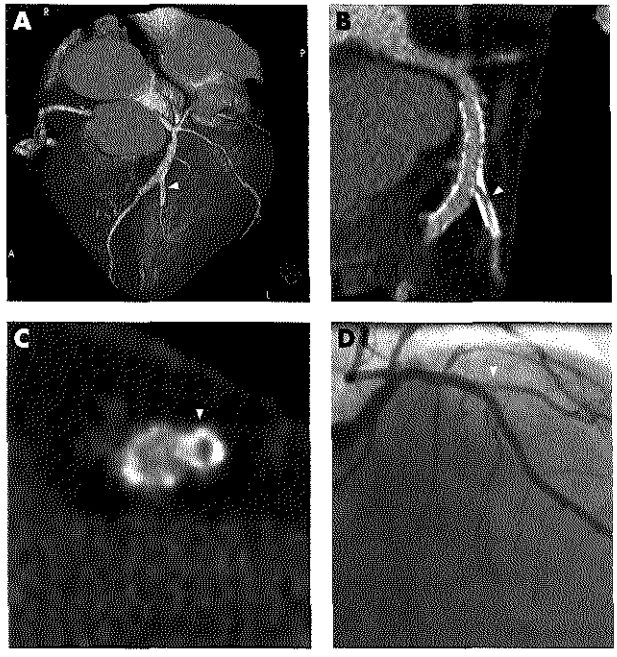


Figure 3. Bifurcations. Patient with in-stent restenosis 6 months after crush-stenting. (A) A volume-rendered DSCT-CA image shows bifurcation stenting of the left anterior descending artery (LAD) and second diagonal branch. The stent in the diagonal branch (side branch) has a diameter of 2.25 mm; the stent in the LAD (main branch) has a diameter of 4 mm. (B) MPR image, (C) MPR cross-section obtained at the level of the carina, and (D) corresponding conventional angiogram demonstrate restenosis in the diagonal branch (arrowhead); the main branch is patent. In (B), note the typical CT appearance of the crush technique, characterised by three layers of metal crushed against the ostium of the side branch. MPR, multiplanar reconstruction.

It may be argued that restenosis occurs more frequently in patients with complex lesion characteristics than in patients with simple lesions (25). This might have led to an overestimation of sensitivity in our *complex configuration* subgroup. However, the difference between the frequency of restenosis in our *simple* and *complex configuration* subgroups was not statistically significant.

STENT DIAMETERS

We found that stent diameter was the most important feature influencing the diagnostic performance of coronary CT angiography. This is in keeping with the findings of Gilard *et al.* (8) and of Rixe *et al.*, (13) who performed 16-slice CT coronary angiography and 64-slice CT coronary angiography, respectively, in patients with low heart rates. In those studies, however, up to 50% of the stents were judged unevaluable. With DSCT-CA, we judged unevaluable only 5% (n=9) of the stents, and found a low rate of false negatives irrespective of stent diameter (NPV in all stents = 98%) NPV in stents ≤2.75 mm = 90%. When stent diameter was ≤2.75 mm, DSCT-CA had a high rate of false positives (specificity = 64%; PPV = 52%) and could not predict with certainty the presence of restenosis; in particular, the specificity of DSCT-CA in this subgroup was significantly lower than that obtained in stents ≥3.5 mm (OR= 6.14; 99%CI: 1.52 to 9.79). Therefore our study confirms that DSCT-CA is not a suitable gatekeeper to conventional angiography in symptomatic patients with ≤2.75 mm stents.

In a recent study, Cademartiri *et al* (4) reported the relationship between diagnostic accuracy of 64-slice CT and stent size in terms of the rate of false diagnosis (false positives and false negatives). In contrast to our findings, the rate of false diagnosis reported in that study did not decrease with increasing stent diameter. In stents <3 mm, the rate of false diagnosis was 6.1%; in 3 mm stents, the rate of false diagnosis was 1.6%; and, surprisingly, in stents >3 mm, the rate of false diagnosis was 12%. An explanation of these findings compared with our study is that only patients with stents larger than 2.5 mm were included. Secondly, complex stent configurations such as overlapping stents and bifurcation stenting were not included in that study, which may have led to an overestimation of the diagnostic performance in smaller stents. Lastly, a 64-slice CT scanner was used, rather than the dual source CT scanner in this study.

It is conceivable that future developments in CT technology might further increase the diagnostic performance in patients with stents by improvements in spatial (eg, flat panel technology) and temporal resolution.

TOTALLY OCCLUDED STENTS

Totally occluded stents might be easier to recognise on DSCT-CA. In our sample, 17 stents were totally occluded. Overall, the analysis after exclusion of totally occluded segments yielded similar sensitivity, specificity and NPV but lower PPV (Table 2).

STUDY LIMITATIONS

We examined a selected symptomatic patient cohort; applicability to a wider population may therefore yield different results. This limitation was inevitable in order to compare DSCT-CA with the reference technique, that is, conventional coronary angiography.

X ray radiation exposure is a general limitation of multi-slice CT coronary angiography (26 27). However, using *x*-ray tube modulation, full dose radiation may be given for a shorter duration of the cardiac cycle than used in this study. Radiation dose is further reduced by automated pitch adaptation with higher heart rates. Other widely accepted imaging techniques, such as technetium sestamibi scans, may deliver radiation doses as high as 20 mSv (26 27).

CONCLUSIONS

This study shows that, in patients with recurrent chest pain after stent implantation, DSCT-CA performs well in the detection of in-stent restenosis. Stent diameter is an important predictor of DSCT-CA diagnostic performance; when stent diameter is ≤2.75 mm, the technique is associated with frequent false positives. However, due to the high NPV, DSCT-CA reliably rules out in-stent restenosis irrespective of stent size.

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PART 3

CLINICAL APPLICATION OF CT CORONARY ANGIOGRAPHY

CHAPTER 6

DIAGNOSTIC PERFORMANCE OF EXERCISE BICYCLE TESTING AND SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY: COMPARISON WITH 64-SLICE COMPUTED TOMOGRAPHY CORONARY ANGIOGRAPHY

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ABSTRACT

OBJECTIVE: The aim of this study was to conduct a comparison of the diagnostic performance of exercise bicycle testing and single-photon emission computed tomography (SPECT) with computed tomography coronary angiography (CTCA) for the detection of obstructive coronary artery disease (CAD) in patients with stable angina.

METHODS: 376 symptomatic patients (254 men, 122 women, mean age 60.4 ± 10.0 yrs) referred for noninvasive stress testing (exercise bicycle test and/or SPECT) and invasive coronary angiography were included. All patients underwent additional 64-slice CTCA. The diagnostic performance of exercise bicycle testing (ST segment depression), SPECT (reversible perfusion defect) and CTCA (≥ 50% lumen diameter reduction) was presented as sensitivity, specificity, positive and negative predictive value (PPV and NPV) to detect or rule out obstructive CAD with quantitative coronary angiography as reference standard. Comparisons of exercise bicycle testing versus CTCA (n=334), and SPECT versus CTCA (n=61 were performed.

RESULTS: The diagnostic performance of exercise bicycle testing was significantly (*P* -value <0.001) lower compared to CTCA: sensitivity of 76% (95% CI, 71 to 82) vs. 100% (95% CI, 97 to 100); specificity of 47% (95% CI, 36 to 58) vs. 74% (95% CI, 63 to 82). We observed a PPV of 70 (95% CI, 65-75) vs. 91 (95% CI, 87-94); and NPV of 30% (95%, 25 to 35) vs. 99% (95%, 90 to 100). There was a statistically significant difference in sensitivity (*P* -value <0.05) between SPECT and CTCA: 89% (95% CI, 75 to 96) vs. 98% (95% CI, 87 to 100); but not in specificity (*P* -value >0.05): 77% (95% CI, 50 to 92) vs. 82% (95% CI, 56 to 95). We observed a PPV of 91 (95% CI, 77-97) vs. 93 (95% CI, 81-98); and NPV of 72% (95%, 46 to 89) vs. 93% (95%, 66 to 100).

CONCLUSIONS: SPECT and CTCA yielded high diagnostic performance compared to traditional exercise bicycle testing for the detection and rule out of obstructive CAD in patients with stable angina.

INTRODUCTION

Exercise bicycle testing represents a widely available and inexpensive diagnostic modality and was part of the initial assessment in 76% of patients with suspected angina in the recent Euro Heart Survey [1, 2]. However, exercise bicycle testing is limited in the prediction of adverse events with a reported 47% of events occurring during follow-up in patients with a negative exercise bicycle test result [3]. Nuclear myocardial perfusion imaging (MPI) using single-photon emission computed tomography (SPECT) allows the noninvasive assessment of the hemodynamic significance of coronary artery stenoses by the detection of myocardial ischemia and provides complementary information for risk stratification [4].

Computed tomography coronary angiography (CTCA) has rapidly emerged as an alternative noninvasive modality for the diagnosis of CAD. The diagnostic performance of CTCA on a per patient level is high with sensitivities ranging from 93% to 100% and specificity ranging from 82% to 96%. In particular, CTCA yields a high negative predictive value to reliable rule out of the presence of significant coronary stenosis [5, 6, 7, 8, 9, 10, 11, 12]. Similar to nuclear MPI, recent studies reported the incremental value CTCA in predicting all-cause mortality in symptomatic patients [13, 14, 15].

In this study, we performed a comparison of the diagnostic performance of exercise bicycle testinging with CTCA, and SPECT with CTCA, respectively, to detect obstructive coronary artery disease using invasive coronary angiography (ICA) as the standard of reference.

METHODS

STUDY DESIGN

We evaluated 376 symptomatic patients (254 men; 122 women, mean age 60.4±10.0) who were referred for stress testing (exercise bicycle test and/or SPECT) and ICA based on gender, age, type (typical, atypical or nonanginal) and severity of chest pain. Typical angina was defined when the following three characteristics were present: 1) sub-sternal discomfort 2) precipitated by physical exertion or emotion and 3) relieved with rest or nitroglycerine within 10 minutes. Atypical angina pectoris was defined when only two out of these three symptom characteristics were met. Nonanginal chest pain was defined when only one was met or absence of the described symptoms.

All patients underwent additional CTCA irrespective of the clinical judgment and stress test outcome as part of a running research protocol. The study protocol was approved by the institutional review board of the Erasmus University Medical Center and informed consent was obtained in all patients.

Patient Population

The study population was obtained from July 2004 until September 2008. Patients with acute coronary syndromes, previous history of percutanous coronary stent placement, coronary artery bypass surgery and prior myocardial infarction were excluded from the study.

Specific CT related exclusion criteria were impaired renal function (serum creatinine>120 μmol/l), persistent arrhythmias, inability to perform a breath hold of 15 seconds, or known allergy to Iodinated contrast material.

Exercise Bicycle Test

Patients underwent exercise bicycle testinging in the absence of contraindications (left bundle branch block, paced rhythm, the Wolff-Parkinson-White syndrome, left ventricle hypertrophy, electrolyte imbalance, intraventricular conduction abnormalities, use of digitalis, or severe aortic stenoses [16]. The exercise bicycle test was interpreted blinded to the CTCA and ICA findings. The exercise bicycle test result was considered positive if the electrocardiogram showed horizontal or down-sloping ST-segment depression or elevation [≥1 mm (0.1-mV) for ≥60-80 ms after the end of the QRS complex] [16]. The exercise bicycle test result was considered equivocal if ischemic ST depression was absent but heart rate did not reach 85% of the maximum predicted for age and gender, if nondiagnostic ST-segments were present during exercise (0.5- to 0.9-mm horizontal ST-segment depression, ST-segment depression with slight upslope, baseline ST-segment and T-wave abnormalities with nondiagnostic changes on stress) or exercise capacity was limited [16, 17].

Single-photon Emission Computed Tomography (SPECT)

SPECT image acquisition and reconstruction was performed as described previously [18, 19]. A dose of 370 MBq of ^{99m}Tc-sestamibi (Cardiolite; Bristol-Myers Squibb Pharma Belgium, Brussels, Belgium) was administered intravenously approximately 1 minute prior to termination of the stress test. For studies performed with the patient at rest, 370 MBq of sestamibi was injected at least 24 hours after the stress test. SPECT images were acquired with a Gammasonics single-head Rota camera (Orbiter; Siemens, Iselin, NJ) without attenuation or scatter correction, by using a low-energy all-purpose collimator. The SPECT images were interpreted blinded to the CTCA and ICA findings. A reversible perfusion defect was defined as a perfusion defect on stress images that partially or completely resolved at rest. A fixed perfusion defect was defined as a perfusion defect on stress images that persisted on rest images. Findings were considered as abnormal in the presence of a fixed and/or reversible perfusion defect.

Computed Tomography Coronary Angiography (CTCA)

The first enrolled patients (n=119) underwent 64-slice CTCA (Sensation 64, Siemens Healthcare, Forchheim, Germany) from October 2004 to March 2006. Patients with a heart rate exceeding 65 bpm received either additional oral or intravenous beta-blockers. The subsequent 257 patients underwent dual-source CTCA (Definition, Siemens Healthcare, and Forchheim, Germany) from April 2006 to September 2008. Patient preparation, scan protocol and image reconstruction algorithm for 64-slice and dual-source CT scanners are presented in the Appen-

dix Table. The CTCA images were interpreted blinded to the results of the stress test or ICA. Segments distal to a chronic total occlusion were excluded. Segments were scored as having obstructive CAD if there was ≥ 50% diameter reduction of the lumen by visual assessment. Segments distal to a chronic total occlusion were excluded.

Invasive Coronary Angiography (ICA)

Four experienced cardiologists, unaware of the results of the stress test or CTCA, analyzed all coronary segments using a modified 17-segment AHA classification [20]. Segments were visually classified as normal (smooth parallel or tapering borders; visually less than 20% narrowing) or as having non-significant or significant coronary obstruction (visually more than 20% narrowing). The stenoses visually scored as having more than 20% narrowing were quantified by a validated quantitative coronary angiography (QCA) algorithm (CAAS, Pie Medical, Maastricht, the Netherlands) [21] and classified as significant if the lumen diameter reduction exceeded ≥50%.

Statistical Analysis

Statistical analyses were performed using SPSS (version 12.1. SPSS Inc Chicago Ill. USA). Categorical patients' demographics and characteristics were expressed as numbers and percentages. Continuous variables were expressed as mean (standard deviation).

The pretest probability of having obstructive CAD was calculated using the Duke Clinical Score, which includes types of chest discomfort, age, gender and traditional risk factors [22, 23] and was expressed as mean (standard deviation).

Diagnostic performance and predictive value of exercise bicycle testing, SPECT and CTCA for the diagnosis of obstructive CAD compared to the reference standard was evaluated on a per patient level and expressed as sensitivity, specificity, positive and negative predictive value (PPV and NPV) and their corresponding 95% confidence intervals, and positive and negative likelihood ratios (LR).

Four comparisons were performed; exercise bicycle testing (conclusive outcome) versus CTCA; exercise bicycle testing (conclusive outcome) and SPECT versus CTCA; exercise bicycle testing (conclusive and inconclusive outcome) versus CTCA; and SPECT versus CTCA. An intention to diagnose design was used: in patients with inconclusive exercise bicycle testing outcome without further testing, the test was scored as a positive outcome. In patients with inconclusive exercise bicycle test outcome with subsequent SPECT, both test results were independently evaluated in the analysis of the diagnostic performance of exercise bicycle test (conclusive outcome) and SPECT, respectively.

The McNemar test was performed to compare the sensitivities and specificities for CTCA versus exercise bicycle testing (conclusive outcome), exercise bicycle testing (conclusive outcome) and SPECT, exercise bicycle testing (conclusive and inconclusive outcome) and SPECT, respectively. Additional agreement analyses between the four comparisons were performed with ICA as reference standard.

RESULTS

Patient demographics (n=376) are listed in Table 1. A total of 334 (89%, 334/376) enrolled patients underwent exercise bicycle testing and 258 (77%, 258/334) patients demonstrated a conclusive outcome. In 76 (23%, 76/334) patients, exercise bicycle testing was inconclusive and 19 (25%, 19/76) patients were subsequently referred to SPECT. In the remaining 57 (75%, 57/76) patients with inconclusive exercise bicycle testing without further testing, the test result was scored as positive for CAD. A total of 42 (11%, 42/376) enrolled patients were directly referred to SPECT. SPECT outcome was conclusive in all patients.

DIAGNOSTIC PERFORMANCE

The overall prevalence of disease was 73% (276/376). ICA showed absence of disease in 10% (39/376), nonsignificant disease in 16% (61/376), single-vessel disease in 36% (135/376) and multi-vessel disease in 38% (141/376) of patients.

The diagnostic performance for the detection of obstructive CAD on a per patient level with QCA as standard of reference is presented in Table 2.

In patients with a conclusive exercise bicycle testing (n=258), sensitivity of CTCA (99%) was significantly (*P*-value <0.001) higher than of exercise bicycle testing (72%). No significant difference (*P*-value = 0.082) was found for specificity between the two modalities: 57% for exercise bicycle testing and 71% for CTCA. Including patients with inconclusive exercise bicycle testing (n=334) both sensitivity and specificity were significant (*P*-value <0.001) higher for CTCA compared to exercise bicycle testing: 100 % and 74% for CTCA, respectively, and 76% and 47% for exercise bicycle testing (conclusive and inconclusive outcome), respectively. In patients with a conclusive stress test (exercise bicycle testing or SPECT; n=319) the sensitivity was significant higher (*P*-value <0.001) for CTCA (99%) compared to the stress test, exercise bicycle testing or SPECT (75%). There was no significant difference (*P*-value = 0.07) in specificity between CTCA and stress test: 74% and 61% respective-

Table 1. Patient Demographics (n=376).

N	376
Typical angina	191 (50)
Atypical angina	93 (25)
Nonanginal chest pain	92 (25)
Men	254 (68)
Age (yrs)*	60.4 ± 10.0
BMI (kg/m²)*	27.3 ± 4.1
Risk factors	
Hypertension†	170 (45)
Hypercholesterolemia‖	199 (53)
Diabetes mellitus ‡	56 (15)
Smoker	88 (23)
Family history of CAD ŧ	64 (17)
Obesity ∓	79 (21)

* Mean and standard deviation. †Blood pressure 140/90 mm Hg or treatment for hypertension. ‖ Total cholesterol >180 mg/dl or treatment for hypercholesterolemia. ‡ Treatment with oral antidiabetic medication or insulin. ŧ Family history of coronary artery disease (CAD), having first- or second-degree relatives with premature CAD (age<55 years). ∓ Body mass index (BMI) > 30 kg/m². *Median and quartiles. Values are n (%) unless otherwise indicated.

Table 2. Diagnostic Performance and Predictive Value of Exercise bicycle test, SPECT and CTCA for the Detection of Obstructive CAD (patient-based analysis).

	Prevalence, %	n	TP	TN	FP	FN	Sensitivity %	Specificity %	PPV, %	NPV, %	+LR	-LR
Exercise Bicycle Test (conclusive outcome)	76	258	140	36	27	55	72 (65-78)	57 (44-69)	84 (77-89)	40 (30-50)	1.68	0.49
CTCA	76	258	194	45	18	1	99 (97-100)	71 (58-82)	92 (87-95)	98 (87-100)	3.48	0.01
Exercise Bicycle Test (conclusive outcome) and SPECT	75	319	179	49	31	60	75 (69-80)	61 (50-72)	85 (80-90)	45 (36-55)	1.93	0.41
CTCA	75	319	237	59	21	2	99 (97-100)	74 (63-83)	92 (88-95)	97 (88-99)	3.77	0.01
Exercise Bicycle Test (conclusive and inconclusive outcome)	74	334	188	41	47	58	76 (71-82)	47 (36-58)	70 (65-75)	30 (25-35)	1.43	0.51
CTCA	74	334	245	65	23	1	100 (97-100)	74 (63-82)	91 (87-94)	99 (90-100)	3.81	0.01
SPECT	72	61	39	13	4	5	89 (75-96)	77 (50-92)	91 (77-97)	72 (46-89)	3.77	0.15
CTCA	72	61	43	14	3	1	98 (87-100)	82 (56-95)	93 (81-98)	93 (66-100)	5.53	0.03

+LR indicates positive likelihood ratio; -LR, negative likelihood ratio; N, number; TP, true positives; TN, true negatives; FP, false positives; FN; false negatives; NPV, negative predictive value; PPV, positive predictive value. Values in parentheses represent upper and lower bound for 95% confidence interval.

ly. In patients who underwent SPECT (n=61) a significant difference was found for sensitivity (*P*-value = 0.021), but not for specificity (*P*-value = 1.0) between SPECT and CTCA. Sensitivity was 89% and 98% for SPECT and CTCA, respectively. Specificity was 77% and 82% for SPECT and CTCA, respectively.

Agreement analysis

The agreement between exercise bicycle testing and CTCA, and SPECT and CTCA, respectively, with ICA as reference standard is presented in Table 3.

Exercise bicycle test and CTCA

In patients who underwent exercise bicycle testing (conclusive and inconclusive outcome), there was agreement with CTCA in 72% of patients (239/334). The agreement between a true positive exercise bicycle test and CTCA outcome was 76% (187/246) in the presence of obstructive CAD at ICA. The agreement between a true negative exercise bicycle test and CTCA outcome was 39% (35/88) in the absence of obstructive CAD at ICA. In patients with a false negative exercise bicycle test outcome, the presence of obstructive CAD was correctly demonstrated by a positive CTCA in all patients (100%, 58/58). A negative CT scan correctly ruled out the presence of CAD in 64% (30/47) of patients with a false-positive exercise bicycle test outcome. Exercise bicycle testing correctly identified one patient with obstructive CAD and 6 patients without obstructive CAD, respectively, who were misdiagnosed with CTCA.

SPECT and CTCA

In patients who underwent SPECT, there was agreement with CTCA in 85% of patients (52/61). The agreement between a true positive SPECT and CTCA was 86% (38/43) in the presence of obstructive CAD at ICA. The agreement between a true negative SPECT and CTCA was 86% (12/14) in the absence of obstructive CAD at ICA. In 5 patients with a false negative SPECT outcome, the presence of obstructive CAD was correctly demonstrated by a positive CTCA in all patients. A negative CT scan correctly ruled out the presence of CAD in two patients with a false-positive SPECT outcome. SPECT correctly identified one patient with obstructive CAD who was misdiagnosed with CTCA.

DISCUSSION

The diagnosis of ischemia remains challenging and extensive effort is invested to improve the noninvasive diagnostic work-up and selection of patients in need for catheterization and possible percutanous catheter treatment. Stress testing prior to percutanous coronary intervention has been associated with shorter hospital stays, and lower rates of revascularization without adverse effects on cardiac death or myocardial infarction [24, 25].

Table 3. Agreement Analysis between CTCA and Exercise Bicycle Test, and CTCA and SPECT (patient based analysis).

N = 258		Exercise bicycle test (conclusive outcome)			
		TP	**TN**	**FP**	**FN**
CTCA	TP (n= 194)	139			55
	TN (n= 45)		30	15	
	FP (n=18)		6	12	
	FN (n=1)	1			0

N = 319		Exercise bicycle test (conclusive outcome) and SPECT			
		TP	**TN**	**FP**	**FN**
CTCA	TP (n= 237)	177			60
	TN (n= 59)		42	17	
	FP (n= 21)		7	14	
	FN (n= 2)	2			0

N = 334		Exercise bicycle test (conclusive and inconclusive outcome)			
		TP	**TN**	**FP**	**FN**
CTCA	TP (n= 245)	187			58
	TN (n= 65)		35	30	
	FP (n= 23)		6	17	
	FN (n= 1)	1			0

N = 61		SPECT			
		TP	**TN**	**FP**	**FN**
CTCA	TP (n= 43)	38			5
	TN (n= 14)		12	2	
	FP (n= 3)		1	2	
	FN (n= 1)	1			0

N indicates number; TP, true positives; TN, true negatives; FP, false positives; FN; false negatives; NPV, negative predictive value; SPECT, single photon emission computed tomography

For reasons of availability and costs, traditionally, exercise ECG using treadmill or bicycle testing represents the first-line test to diagnose inducible ischemia in patients presenting with anginal complaints. Exercise bicycle testing should be conducted in patients not taking anti-ischemic drugs, but this may not always be possible or considered safe [16]. Exercise bicycle testing is not of diagnostic value in the presence of a left bundle branch block, paced rhythm and Wolff-Parkinson-White syndrome that prevent reliable evaluation of the ECG changes during stress.

Lower specificity and positive predictive value are reported in patients with resting ECG abnormalities, in the presence of left ventricle hypertrophy, electrolyte imbalance, or intraventricular conduction abnormalities and digitalis use. The exercise bicycle test is less sensitive and specific in women, in detecting single vessel disease, right coronary or circumflex artery disease, and in the presence of serial stenoses or extensive collaterals [26].

Nuclear MPI using SPECT has several advantages over exercise bicycle testing including superior diagnostic performance [16], quantification and localization of areas of ischemia, and incremental value for risk stratification [19]. Despite the introduction of X-ray-based attenuation correction and gated scanning, SPECT remains susceptible to a variety of artefacts (respiratory motion, spill-over from gut or liver activity) resulting in low PPV for identifying areas of ischemia in need for revascularization.

CTCA allows direct visualization of the coronaries and numerous studies have demonstrated a high diagnostic performance of CTCA in selected patient populations [5, 6, 7, 8, 9, 10, 11, 12]. The high NPV (range 95-100%) permits CTCA to act as reliable gate keeper to discharge patients from further testing [27]. The current drawback of CTCA is the insufficient spatial resolution resulting in lower PPV in particular in the presence of calcium.

We performed a comparison of exercise bicycle testing with CTCA, and SPECT with CTCA, respectively, using ICA as reference standard. The number of inconclusive exercise bicycltest results (23%) is in line with reported values in literature [28]. The sensitivity of exercise bicycle testing (72-76%) is similar to outcome of a large meta-analysis (sensitivity 68%, specificity 77%) [22], specificity is lower (47-57%). Dewey et al. presented comparable results in a head-to-head comparison of exercise ECG and MSCT in 80 patients [29].

We found that SPECT and CTCA yielded a high diagnostic performance (sensitivity of 89% and 98%; specificity of 77% and 82%) that was superior to exercise bicycle testing (sensitivity 76%, specificity 47%). We observed a reasonable agreement (76%) between a true positive exercise bicycle testing and CTCA and only a fair agreement (39%) was found between a true negative exercise bicycle testing and CTCA. The agreement was good (86%) between a true positive SPECT and CTCA and only modest (76%) between a true negative SPECT and CTCA.

Our results are partly in line with reported studies on comparison between SPECT and CTCA that showed a good agreement (range 86-96%) in the absence of obstructive CAD [30, 31, 32, 33, 34]. However, these studies demonstrated a lower agreement (range 50-67%) for the detection of lesions with CTCA that induced myocardial perfusion defects. The discrepancies in agreement should be interpreted in the context of the pretest risk of disease and the standard of reference. Furthermore, the standard of reference ICA was not used in all patients with the exception of one study [30].

Which modality will represent the first-line test in the diagnostic work-up of patients with stable angina is largely unknown and depends on its relative costs and availability, the pretest risk of

disease in the cohort to be examined, and the number of patients that can be identified as not needing further evaluation. The exercise bicycle test is widely availably, not costly and safe compared to SPECT and CTCA, and despite its inferior diagnostic performance, may represent the first line test in patients with a low pretest risk. SPECT and CTCA have superior diagnostic performance, but are associated with higher costs and radiation exposure, and may represent more appropriate initial tests in patients with an intermediate to high pretest risk. In patients with stable angina, both normal CTCA and SPECT have a low risk of hard coronary events (cardiac death or nonfatal myocardial infarction) obviating the need for catheterization or further testing [14, 19, 35, 36, 37].

SPECT as initial test may identify jeopardized ischemic myocardium on a per patient level [38], which fulfills the recommendations of the guidelines prior to revascularization. However, several studies indicated that SPECT only moderately guides revascularization treatment of the ischemia-related vessel [39, 40, 41]. CTCA could add valuable information to MPI by allocating perfusion defects to specific epicardial coronary vessels. However, there is a known discrepancy in hemodynamic significance of intermediate lesions with a luminal diameter stenosis between 40% and 70% [30, 42, 43, 44, 45]. Luminal diameter stenosis measurement does not always reflect coronary artery resistance as it neglects specific lesion characteristics, vasomotor tone or presence of coronary collateral flow that may significantly affect myocardial perfusion [46]. Individual variations in coronary anatomy may also contribute to inadequate allocation of perfusion defects to corresponding coronary arteries [31]. On the other hand, in case of multivessel disease lack of perfusion defects at SPECT in patients with obstructive lesions at ICA may be attributed to a balanced reduction in myocardial perfusion owing to the compromised coronary vasodilator reserve in territories supplied by angiography stenoses and thereby reducing the heterogeneity of flow between "normal" and "abnormal" zones [47].

The potential of 2D/3D image fusion techniques or hybrid scanners (SPECT/CT) to correctly link coronary stenoses at CTCA to perfusion defects to resolve inadequate allocation of perfusion defects is now being explored. The clinical application of cardiac hybrid imaging was hampered due to the associated high radiation exposure to the patient (up to 40 mSv) [48] but technical advances now permit hybrid imaging below 5 mSv with low-dose CTCA using prospective ECG triggering combined with stress-only SPECT [49, 50]. Further investigation is needed to evaluate the diagnostic performance of SPECT/CT to accurately allocate and guide treatment of the target vessel.

LIMITATIONS

For the comparison SPECT versus CTCA, analyses were limited to small sample size.

The possibility of referral bias may occur when patients are referred to the reference test based on the results of the noninvasive test under investigation. Sensitivity may be inflated and specificity deflated if patients with a positive test result are more likely to be verified.

CONCLUSIONS

SPECT and CTCA yielded a high diagnostic performance compared to traditional exercise bicycle testinging for the detection and rule out of obstructive CAD in patients with stable angina. Future studies are needed to evaluate the clinical value of traditional noninvasive diagnostic tests compared to new test such as CTCA or hybrid CTCA/SPECT taking into account the pretest risk, availability, radiation exposure and cost-effectiveness.

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Appendix 1. CTCA Protocol.

Patient preperation	**64-slice CT** [a]	**Dual-Source CT** [b]
Betablockers (dose, oral)	Yes	No
Lorazepam (dose, oral)	Yes	No
Nitroglycirine (0.4mg/dose, sublingual)	No	Yes
Scan parameters		
No. of tubes	1	2
No. of detectors	32x2 - 64	32x2 - 64
Collimation (mm)	32x2x0.6 mm [c]	32x2x0.6 mm [c]
Gantry rotation time (ms)	330	330
Effective temporal resolution (ms)	165 ms [d]	83 ms [d]
pitch	0.20	0.20-0.53
kV	120	120
Full tube current (mA)	800-900	625
ECG pulsing	Yes	Yes
Scan time range (s)	15-20	5-15
Bolus tracking	yes	yes
Contrast volume (mL)	50-120	60-100
Contrast agent (mgI/mL)	400	370
Saline chaser volume (mL)	40	40
Injection rate (mL/sec)	4.0-5.0	5.5
Image Reconstruction		
Effective slice width (mm)	0.75	0.75
Reconstruction interval (mm)	0.4	0.4
Field of view (mm)	180	180
Convolution filter	medium/sharp	medium/sharp

[a] Sensation®, Siemens, Forchheim, Germany;
[b] Definition ®, Siemens, Forchheim, Germany;
[c] Z-sharp® Technology Siemens, Forchheim, Germany;
[d] Single-segmental reconstruction algorithm

CHAPTER 7

DIAGNOSTIC ACCURACY AND CLINICAL UTILITY OF NONINVASIVE TESTING FOR CORONARY ARTERY DISEASE

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ABSTRACT

BACKGROUND: Computed tomography coronary angiography (CTCA) has become a popular noninvasive test for diagnosing coronary artery disease.

OBJECTIVE: To compare the accuracy and clinical utility of stress testing and CTCA for identifying patients who require invasive coronary angiography (ICA).

DESIGN: Observational study.

SETTING: University medical center in Rotterdam, the Netherlands.

PATIENTS: 517 patients referred by their treating physicians for evaluation of chest symptoms by using stress testing or ICA.

INTERVENTION: Stress testing and CTCA in all patients.

MEASUREMENTS: Diagnostic accuracy of stress testing and CTCA compared with ICA; pretest probabilities of disease by Duke clinical score; and clinical utility of noninvasive testing, defined as a pretest or posttest probability that suggests how to proceed with testing (no further testing if <5%, proceed with ICA if between 5% and 90%, and refer directly for ICA if 90%)

RESULTS: Stress testing was not as accurate as CTCA; CTCA sensitivity approached 100%. In patients with a low (<20%) pretest probability of disease, negative stress test or CTCA results suggested no need for ICA. In patients with an intermediate (20% to 80%) pretest probability, a positive CTCA result suggested need to proceed with ICA (posttest probability, 93% [95% CI, 92% to 93%]) and a negative result suggested no need for further testing (posttest probability, 1% [CI, 1% to 1%]). Physicians could proceed directly with ICA in patients with a high (>80%) pretest probability (91% [CI, 90% to 92%]).

LIMITATIONS: Referral and verification bias might have influenced findings. Stress testing provides functional information that may add value to that from anatomical (CTCA or ICA) imaging.

CONCLUSION: Computed tomography coronary angiography seems most valuable in patients with intermediate pretest probability of disease, because the test can distinguish which of these patients need invasive angiography. These findings need to be confirmed before CTCA can be routinely recommended for these patients.CT coronary angiography (CTCA) has emerged as an alternative technique but its clinical utility is yet unknown.

INTRODUCTION

Invasive coronary angiography (ICA) is the reference standard for diagnosing coronary artery disease (CAD), but it is expensive. Noninvasive tests, such as exercise electrocardiography (ECG), single-photon emission computed tomography (SPECT), or stress echocardiography, are less expensive but also less accurate (1–3). Computed tomography coronary angiography (CTCA) is a newer noninvasive test that has been shown to be especially accurate for excluding coronary artery disease (4–11). However, it is unclear how CTCA performs in relation to existing noninvasive tests and how it should be used along with other tests in the management of patients with chest symptoms.

Because the clinical utility of a test depends not only on its diagnostic accuracy but also on the pretest probability of disease in a population, we evaluated the diagnostic accuracy and clinical utility of stress testing and CTCA for identifying which patients with chest symptoms should receive ICA on the basis of their pretest probability of disease.

METHODS

Study design and Patients

We approached and prospectively recruited patients with chest symptoms who were referred to our medical center for stress testing (exercise ECG or SPECT) and ICA by their treating physicians. We recruited patients during 2 enrollment periods: 2004 to 2006, during which all 297 eligible patients underwent stress testing, CTCA, and ICA, and 2006 to 2008, during which all 220 patients who met eligibility criteria underwent stress testing and CTCA.

In the second group, 141 patients had a negative stress test result and a normal CTCA result; we did not refer these patients for ICA because new data (12–17) indicated an extremely low probability of either obstructive coronary artery lesions or adverse events in such patients, and we therefore considered it unethical to proceed with ICA. We included these patients in the study and classified them as not having obstructive CAD (true-negative results).

We considered patients ineligible for the study if they had acute coronary syndromes or a history of percutaneous coronary stent placement, coronary artery bypass surgery, or myocardial infarction. Patients with other forms of atherosclerotic disease, such as previous nonstent percutaneous intervention or cerebrovascular or peripheral artery disease, were eligible. All diagnostic test results were interpreted by 1 or more readers with more than 5 years of experience, who were blinded to the results of all other tests. The institutional review board of the Erasmus University Medical Center, Rotterdam, the Netherlands, approved our study protocol. We informed patients of the risks of radiation exposure and intravenous administration of iodinated contrast medium and the potential complications associated with CTCA (such as occurrence of contrast extravasation). All patients gave informed consent.

Stress Testing

Stress testing comprised exercise ECG and SPECT. Patients underwent exercise ECG if they had adequate exercise capacity and no contraindications, such as left bundle branch block, paced rhythm, the Wolff–Parkinson–White syndrome, left ventricular hypertrophy, electrolyte imbalance, intraventricular conduction abnormalities, use of digitalis, or aortic stenoses (18). We defined the result as positive if horizontal or down-sloping ST-segment depression ($\geq$ 1 mm) was present; equivocal if ischemic ST-segment depression was absent but heart rate did not reach 85% of the maximum predicted for the patient's age and sex; and negative otherwise.

We referred patients with inadequate exercise capacity, contraindications to ECG stress testing, or equivocal ECG results for pharmacologic SPECT according to standard protocols (19, 20). We considered perfusion defects on stress images to be reversible if they partially or completely resolved at rest and fixed if they persisted on rest images.

We considered both fixed and reversible perfusion defects to be abnormal. We considered pharmacologic SPECT findings to be definitive for patients with equivocal ECG results who had both tests. We classified patients with equivocal ECG stress test results who did not have pharmacologic SPECT (because of test unavailability due to long waiting lists for the test) as having a positive stress test result.

CTCA

Patients were eligible for CTCA if they were not pregnant, had no known allergy to iodine contrast media, and had normal renal function (serum creatinine level < 12 μmol/L [<1.36 mg/dL]) and regular heart rhythms. Patients underwent CTCA as described elsewhere (6, 11, 21). Patients enrolled in the first period had 64-slice (119 patients) or dual-source CTCA (178 patients), and those enrolled in the second period (220 patients) had dual-source CTCA. Dual-source CTCA obtains images more rapidly, which allows them to be reliably obtained in patients with higher heart rates. Appendix Table 1 summarizes the protocols. Two readers analyzed coronary segments by using a modified 17-segment American Heart Association classification (22). They scored segments as demonstrating obstructive CAD if the lumen diameter was reduced by 50% or more on visual assessment. The readers excluded segments distal to a chronic total occlusion. They analyzed all CTCA scans, including all vessels and segments, even if the image quality was poor because of extensive calcification, coronary motion, or breathing artifacts.

ICA

In patients referred for ICA, we used quantitative coronary angiography (QCA) as the reference standard. Patients underwent ICA within 4 weeks of CTCA. Four cardiologists analyzed all coronary segments. Stenoses scored as having more than 20% narrowing on visual assessment were quantified by a validated QCA algorithm (23) and classified as significant if the lumen diameter was reduced by 50% or more.

STATISTICAL ANALYSIS

We used SPSS, version 12.1 (SPSS, Chicago, Illinois), for all statistical analyses. We report categorical variables as numbers and percentages and continuous variables as means (SDs). We express the diagnostic accuracy of stress testing and CTCA compared with ICA as sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios, with corresponding 95% CIs. We determined interobserver variability for the detection of significant stenoses on CTCA by κ statistics and determined intraobserver agreement similarly, on the basis of readings from 100 patients.

We defined a patient's pretest probability of having obstructive CAD by using the Duke clinical score, which uses type of chest discomfort, age, sex, and traditional risk factors to calculate a specific probability and classifies patients as having a low (<25%), intermediate (25% to 75%), or high (>75%) probability of disease (3, 24). We used similar thresholds in our primary analyses, categorizing patients into low (<20%), intermediate (20% to 80%), or high (>80%) pretest probability groups. We altered the thresholds of these categories (to <10%, 10% to 90%, and >90% and to <30%, 30% to 70%, and >70%) to test the sensitivity of our findings to these primary thresholds (25, 26).

We calculated posttest probability as a function of pretest probability according to the Bayes theorem of conditional probability (27). We used the posttest probability of an initial test as the pretest probability for a subsequent test. Pretest and posttest probabilities are expressed as means (95% CIs). We assessed the clinical utility of stress testing and CTCA, alone or combined, assuming that pretest or posttest probabilities of 5% or less indicated that no further diagnostic testing was required, probabilities between 5% and 90% represented uncertainty and indicated that further diagnostic testing was required, and probabilities of 90% or greater indicated direct referral for ICA.

We performed analyses for the overall population and stratified by pretest probability category and enrollment period. To assess the potential effects of verification bias in the second period, we performed an additional analysis with the assumption that 3% of the patients who had negative stress test and CTCA results and were presumed to have no CAD actually did have disease (a 3% false-negative rate) (24).

RESULTS

Of the 612 patients referred for diagnostic work-up who were eligible for the study, 95 were excluded from our final analyses (Figure 1). Table 1 shows demographic characteristics for the remaining 517 patients. Of these, 475 (92%) underwent exercise ECG and 42 (8%) were referred for pharmacologic SPECT because of inability to exercise or preexisting ECG changes.

Table 1. Patient Characteristics and Test Results.

	All Patients (n=517)
Mean age (SD), y	58.9 (10.2)
Men, n (%)	317 (61.3)
Chest pain, n (%) *	
Typical angina	223 (43.1)
Atypical angina	111 (21.5)
Nonanginal chest pain	183 (35.4)
Mean body mass index (SD), kg/m^2	27.3 (4.2)
Risk factors	
Hypertension †	224 (43.3)
Hypercholesterolemia ‡	242 (46.8)
Diabetes mellitus ǂ	68 (13.2)
Smoker	118 (22.8)
Family history of CAD ⊦	98 (19.0)
Obesity ∓	101 (19.5)
Stress test, n (%)	
Exercise ECG	475 (91.9)
Nuclear MPI	61 (11.8)
Both	19 (3.7)
Reference standard ∞	
Prevelance of obstructive CAD, % (n/N)	53 (276/517)
Absence of CAD, n (%)	180 (34.8)
Nonsignificant disease, n (%)	61 (11.8)
Single-vessel disease, n (%)	140 (27.0)
Multi-vessel disease, n (%)	136 (26.3)

CAD = coronary artery disease; CTCA = computed tomography coronary angiography; ECG = electrocardiography; SPECT = single-photon emission computed tomography.

* We defined typical angina as substernal discomfort that was precipitated by physical exertion or emotion and relieved by rest or nitroglycerin within 10 minutes.

We classified chest pain with only 2 of these 3 symptom characteristics as atypical angina pectoris; if only one or none of the characteristics was present, we classified it as nonanginal chest pain.

† Blood pressure of 140/90 mm Hg or treatment for hypertension.

‡ Total cholesterol level >4.66 mmol/L (>180 mg/dL) or treatment for hypercholesterolemia.

ǂ Treatment with oral antidiabetic medication or insulin.

⊦ Patient had first- or second-degree relatives with premature CAD (aged <55 y at diagnosis).

∓ Body mass index >30 kg/m^2.

∞ Invasive coronary angiography; includes patients who were not referred for invasive coronary angiography on the basis of normal stress test and CTCA results.

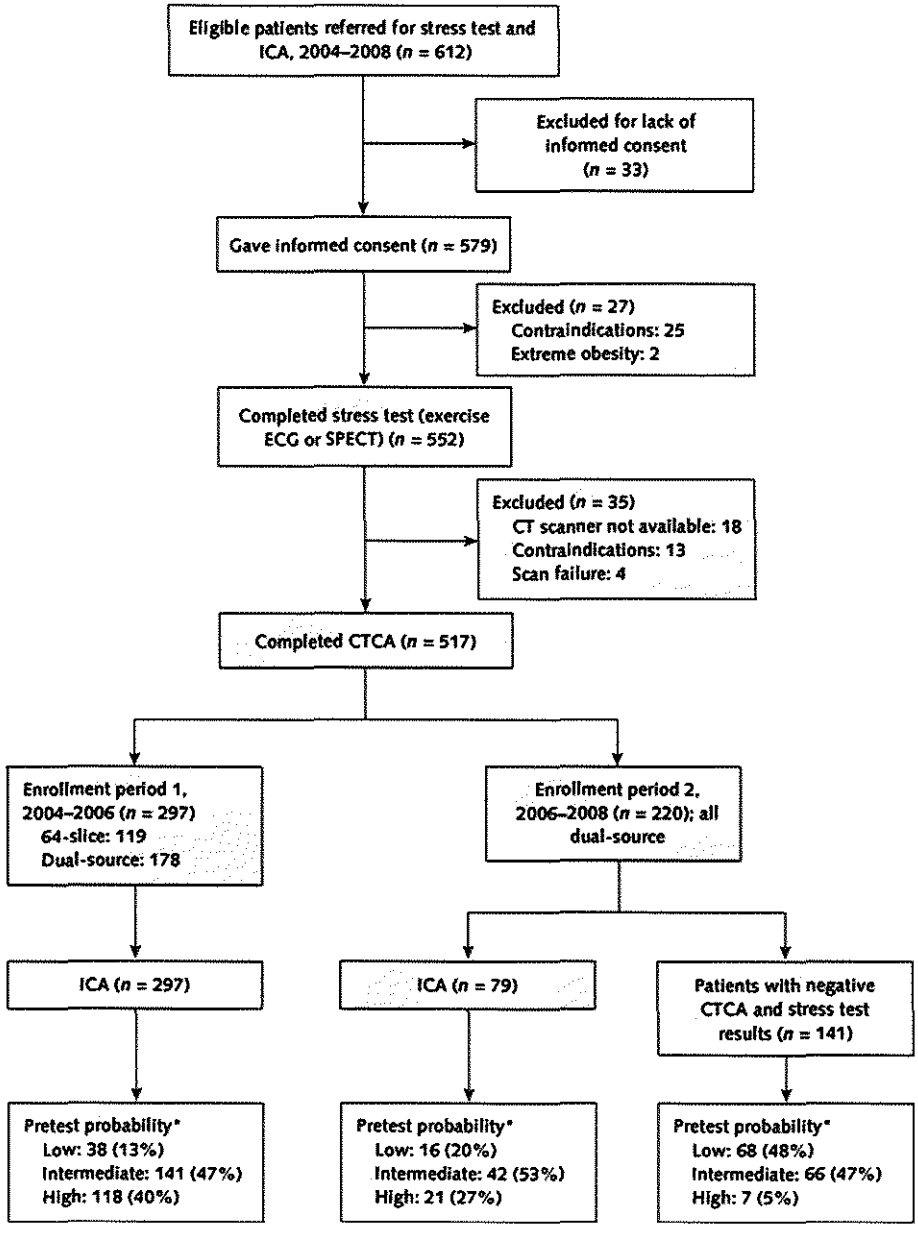


Figure 1. Study Flow Diagram. CT = computed tomography; CTCA = computed tomography coronary angiography; ECG = electrocardiography; ICA = invasive coronary angiography; SPECT = single-photon emission computed tomography. * On the basis of Duke clinical score. We defined low probability as <20%, intermediate as 20% to 80%, and high as >80%.

Of the 475 patients who underwent exercise ECG testing, 76 (16%) had equivocal results. Of these, 19 (25%) underwent additional SPECT, and the 57 (75%) who did not have the test because it was unavailable were classified as being positive for obstructive CAD.

Of the 220 patients enrolled during the second study period, 141 (64%) had both a negative stress test result and a normal CTCA result. We did not refer them for ICA and classified them as not having obstructive CAD (true negatives).

Patients who were not referred for ICA had significantly lower pretest probability and prevalence of disease than those who were referred for ICA (Appendix Table 2).

Appendix Table 3 lists the number of patients with equivocal ECG results, those who underwent SPECT, and those who were not referred for ICA, stratified by pretest probability.

We found no statistically or diagnostically significant changes in estimates of sensitivity and specificity for stress testing or CTCA (Appendix Table 2) in an analysis that assumed 3% prevalence of CAD in patients enrolled in the study's second period who were not referred for ICA because of negative stress testing and CTCA results.

Figure 2. Intention-to-diagnose Strategies in Patients with a Low (<20%) Pretest Probability.
Probability is based on Duke clinical score. CTCA = computed tomography coronary angiography; PTP = posttest probability.

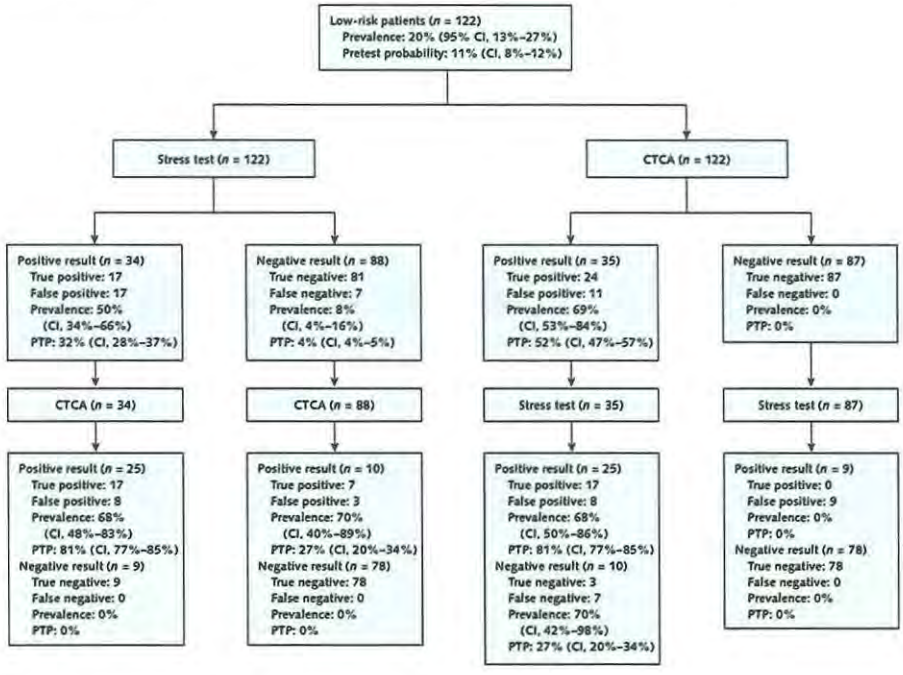


Table 2. Diagnostic Performance and Predictive Value of Stress Testing and CTCA for Detecting Obstructive Coronary Artery Disease (Patient-by-Patient analysis), Using Different Thresholds for Low, Intermediate, and High Pretest Probabilities.

Pretest Probability and Test	Prevalence, % *	Pretest Probability †, %	Patients, n	True-Positives	True-Negatives	False-Positives	False-Negatives	Sensitivity, (95% CI), %	Specificity, (95% CI), %	PPV, (95% CI), %	NPV, (95% CI), %	Positive LR	Negative LR
Stress test													
Overall													
Stress test	53	52	517	216	187	54	60	78 (73-83)	77 (72-83)	80 (75-85)	76 (70-81)	3.49 (2.74-4.45)	0.28 (0.22-0.35)
CTCA	53	52	517	274	215	26	2	99 (97-100)	89 (84-93)	91 (87-94)	99 (96-100)	9.20 (6.40-13.00)	0.01 (0.00-0.03)
Low (<20%) ‡													
Stress test	20	11	122	17	81	17	7	71 (49-87)	83 (76-89)	50 (33-67)	92 (84-97)	4.08 (2.47-6.75)	0.35 (0.19-0.66)
CTCA	20	11	122	24	87	11	0	100 (83-100)	89 (80-94)	69 (50-83)	100 (95-100)	8.91 (5.11-15.53)	0.00 (0.00-0.35)
Intermediate (20-80%) §													
Stress test	53	50	249	104	91	27	27	79 (71-86)	77 (68-84)	79 (71-86)	77 (68-84)	3.46 (1.20-3.20)	0.28 (0.19-0.38)
CTCA	53	50	249	130	110	8	1	99 (95-100)	93 (87-97)	94 (89-97)	99 (94-100)	14.64 (7.50-28.58)	0.01 (0.00-0.06)
High (>80%) ‡													
Stress test	83	91	146	95	15	10	26	79 (70-89)	60 (39-78)	91 (83-95)	37 (23-53)	1.96 (1.20-3.20)	0.36 (0.24-0.53)
CTCA	83	91	146	120	18	7	1	99 (95-100)	72 (50-87)	95 (89-98)	95 (72-100)	3.54 (1.89-6.64)	0.01 (0.00-0.08)

CTCA = computed tomography coronary angiography.

* Patients with coronary artery disease of those tested. For example, 24 of the 122 patients who underwent CTCA had a low pretest probability (<20%), for a prevalence of 19.7% or 20%.

‡ On the basis of Duke clinical score.

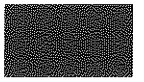
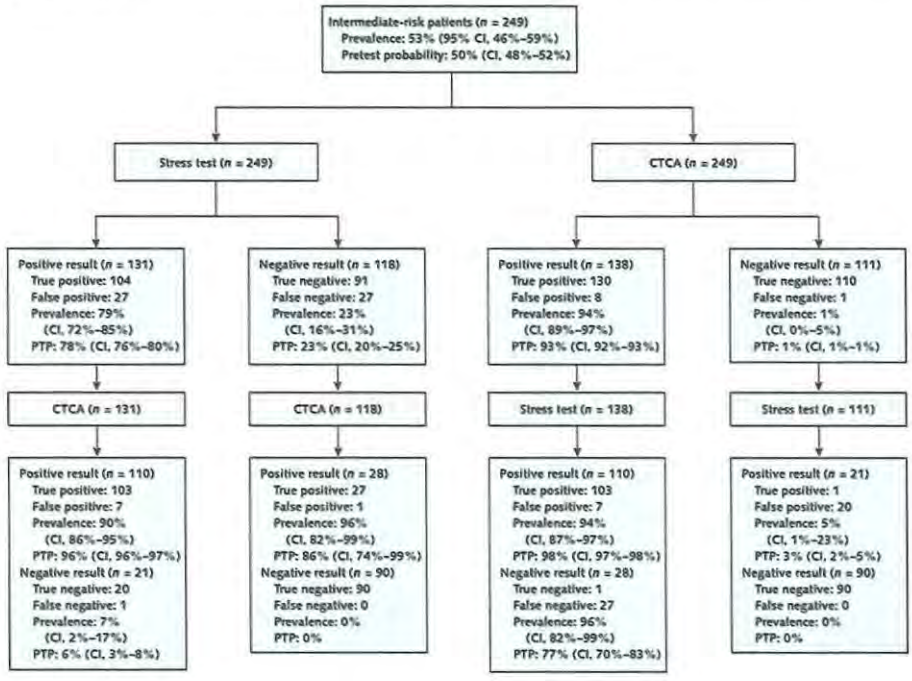


Figure 3. Intention-to-diagnose Strategies in Patients with an Intermediate (20%-80%) Pretest Probability. Probability is based on Duke clinical score. CTCA = computed tomography coronary angiography; PTP = posttest probability.



Diagnostic Accuracy of Stress Testing and CTCA

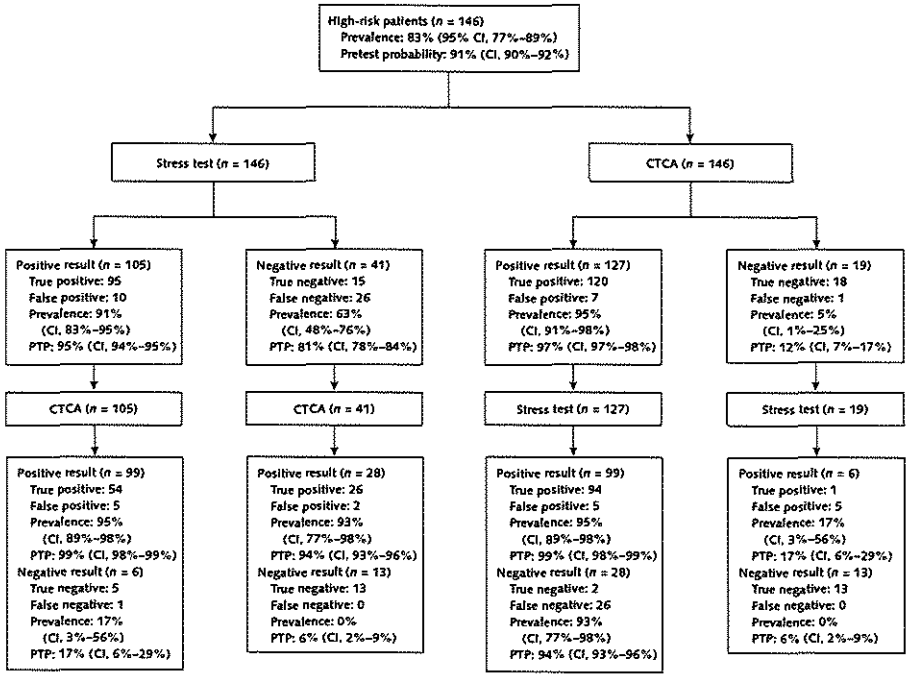
Stress testing was less accurate than CTCA, with lower sensitivity, specificity, predictive values, and likelihood ratios in all pretest groups (Table 2). Stress test likelihood ratios were between 0.1 and 10 for all pretest probability groups. Because CTCA sensitivity approached 100% in all groups, the CTCA negative likelihood ratio was less than 0.1 in all pretest probability groups. The CTCA positive likelihood ratio was greater than 10 only in the intermediate pretest probability group.

Among patients referred for ICA during both enrollment periods, we found no statistically or clinically significant differences in sensitivity or specificity estimates for stress testing and CTCA (Appendix Table 2). Observer variability for detection of significant stenoses by CTCA was good (interobserver κ, 0.91 [95% CI, 87 to 95]; intraobserver κ, 0.98 [CI, 94 to 100]).

Intention-to-Diagnose Work-up

Figures 2 to 4 present posttest probabilities after stress testing and CTCA, combined or alone and used as either an initial test or a subsequent additional test in patients with low, intermediate, and high pretest probabilities. Under the assumption that testing could be stopped for

Figure 4. Intention-to-diagnose Strategies in Patients with a High (>80%) Pretest Probability. Probability is based on Duke clinical score. CTCA = computed tomography coronary angiography; PTP = posttest probability.



probability of 5% or less and that a probability of 90% or greater warranted ICA, patients in the low pretest probability group with an initial negative stress test result (4% posttest probability) or initial negative CTCA result (0% posttest probability) required no further testing (Figure 2).

Patients in the intermediate pretest probability group with an initial positive CTCA result (93% posttest probability) were candidates for ICA, whereas those with an initial negative CTCA result (1% posttest probability) needed no further testing (Figure 3). For patients in the high pretest probability group (91% pretest probability), the Duke clinical score provided sufficient justification to proceed with ICA (Figure 4).

Secondary Analyses

Appendix Table 4 shows the diagnostic accuracy of stress testing and CTCA at pretest thresholds of 10% and 90% and thresholds of 30% and 70%; our findings were similar to those obtained at thresholds of 20% and 80%. Stress test likelihood ratios were between 0.1 and 10 for all pretest probability groups with both sets of alternative thresholds, and because CTCA sensitivity approached 100% in all groups, the CTCA negative likelihood ratio was less than 0.1 in all pretest probability groups with all thresholds. The CTCA positive likelihood ratio was greater

than 10 for the low pretest probability group at the less than 10% and less than 30% thresholds and for the intermediate group at the 30% to 70% but not the 10% to 90% threshold.

Appendix Figures 1 to 6 to present posttest probabilities at pretest probability thresholds of 10% and 90% and thresholds of 30% and 70%. Our findings were nearly identical to those obtained with our primary analyses (Appendix Figures 7 to 9).

DISCUSSION

In this study of the diagnostic accuracy of stress testing and CTCA for patients with chest symptoms and suspected CAD, we found that stress testing was less accurate than CTCA. Clinical utility, defined as a posttest probability sufficient to stop testing (<5%) or proceed directly with ICA (>90%), was similar for stress testing and CTCA in patients with a low pretest probability of disease.

The clinical utility of CTCA was superior to that of stress testing in patients with an intermediate pretest probability, because a positive result conclusively confirmed disease and a negative result conclusively excluded disease in all patients.

A high pretest probability assigned by Duke clinical score was sufficient to proceed with ICA; noninvasive testing only confirmed disease in most of these patients.

Our estimates of the diagnostic accuracy of stress testing and 64-slice CTCA are in concordance with earlier reports. Previous estimates (18) suggest that the sensitivity and specificity of exercise ECG and nuclear stress perfusion are only moderate and may not reliably discriminate between patients who do and those who do not require ICA.

Four recent systematic reviews and 3 recent large, multicenter trials (4, 5, 7, 9, 10, 28, 29) reported sensitivities that ranged from 85% to 99% and specificities that ranged from 88% to 91% by per-patient analysis for 64-slice CTCA. A recent direct comparison of the diagnostic accuracy of ECG stress testing and CTCA in symptomatic patients (30) indicated that CTCA was superior, with higher sensitivity, specificity, and predictive values.

However, diagnostic accuracy is an incomplete measure of the clinical utility of a test, which also depends on whether the probability of disease after testing suggests clear clinical decisions. Because the diagnostic accuracy of a test may differ from its clinical utility in patients with various pretest probabilities of CAD, we examined both stress testing and CTCA in patients with low, intermediate, and high pretest probabilities of CAD. Our findings suggest that an initial stress test might be considered as a first-line test in patients with a low pretest probability of disease, because it is safe, widely available, inexpensive, and—unlike CTCA—does not use ionizing radiation.

Computed tomography coronary angiography was a reliable first-line diagnostic test in patients with an intermediate pretest probability because, unlike stress testing, it yielded sufficient certainty in patients in this group to stop testing or proceed with ICA. In the high pretest probability group, the Duke clinical score provided sufficient certainty (>90%) to proceed with ICA without further noninvasive testing; however, patients in this group often require revascularization, and functional stress testing may therefore still be useful to provide objective evidence of ischemia before revascularization (2, 31–34).

Our study has limitations. Referral bias was present, because patients were recruited into the study from a population referred by their clinicians for diagnostic work-up, including ICA, of their chest symptoms, and the effect of that bias on our findings is uncertain. Verification or work-up bias was probably also present during the second enrollment period, because the results of stress testing and CTCA influenced which patients received ICA (the reference).

However, an analysis that assumed a 3% prevalence of CAD in this subgroup of patients suggested no clinically significant effect of the bias on study estimates.

Our probability thresholds for distinguishing patients with low, intermediate, and high pretest probability of disease were arbitrary. However, we also assessed stress testing and CTCA at different pretest thresholds and found only small differences compared with the 20% and 80% thresholds.

Finally, our study compared both functional stress testing and CTCA with QCA. Anatomical lesions seen on imaging (CTCA and QCA) are not always functionally significant, so the comparisons may have produced estimates of accuracy that make CTCA seem more accurate and clinically useful than it really is. However, CTCA has inferior spatial and temporal resolution compared with ICA, and the techniques vary in their assessment of the severity of stenosis (5). Combining information on coronary anatomy with that of functional ischemia may offer better guidance for patient management decisions. A diagnosis of coronary obstruction requires functional testing to establish the presence of flow reduction, and a diagnosis of functional abnormality requires coronary anatomy data to distinguish between epicardial coronary obstruction and microvascular disease and to identify the presence of left main or 3-vessel disease, which is associated with an unfavorable prognosis and is often undetected by exercise ECG or SPECT (35, 36). Future research should further explore the diagnostic benefit of integrating anatomy imaging and function testing by either multi-imaging fusion techniques or hybrid configurations, such as computed tomography and SPECT or computed tomography and positron emission tomography, both of which have shown promising preliminary results (37, 38).

In summary, our findings suggest a focused role for CTCA testing. Stress testing is sufficient as a first diagnostic test for patients with a low pretest probability of CAD on the basis of their Duke clinical score. Computed tomography coronary angiography plays a more important role in patients with an intermediate pretest probability, in whom the test can distinguish which patients require invasive testing. In patients with a high pretest probability, neither stress testing

nor CTCA offers much additional diagnostic value, and physicians can proceed directly to ICA. Additional studies, including cost– benefit analyses, are needed to confirm our findings before CTCA is accepted as a first-line diagnostic test in patients with an intermediate pretest probability of CAD.

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Appendix Table 1. Computed Tomography Coronary Angiography Protocol.

Parameter	64-slice Computed Tomography *	Dual-Source Computed Tomography †
Patient preperation		
Betablockers (oral dose)	Yes	No
Lorazepam (oral dose)	Yes	No
Nitroglycerin (0.4mg/dose, sublingual)	No	Yes
Scan parameters		
Tubes, n	1	2
Detectors, n	32x2 - 64	32x2 - 64
Collimation, mm	32x2x0.6 mm [c]	32x2x0.6 mm [c]
Gantry rotation time, ms ♯	330	330
Effective temporal resolution, ms ǂ	165 ms [d]	83 ms [d]
Pitch	0.20	0.20-0.53
Tube voltage, kV	120	120
Full tube current, mA	800-900	625
Electrocardiographic pulsing	Yes	Yes
Scan time range, s	15-20	5-15
Bolus tracking	yes	yes
Contrast volume, mL	50-120	60-100
Contrast agent , mgI/mL	400	370
Saline chaser volume, mL	40	40
Injection rate, mL/sec	4.0-5.0	5.5
Image Reconstruction		
Effective slice width, mm	0.75	0.75
Reconstruction interval, mm	0.4	0.4
Field of view, mm	180	180
Convolution filter	medium/sharp	medium/sharp

* Sensation (Siemens, Forchheim, Germany).
† Definition (Siemens, Forchheim, Germany).
♯ Z-sharp (Technology Siemens, Forchheim, Germany).
ǂ Using a single-segmental reconstruction algorithm

Appendix Table 2. Diagnostic Performance and Predictive Value of Stress Testing and CTCA for the Detection of Obstructive Coronary Artery Disease (Patient-by-Patient Analysis).

Test	Prevalence,	Pretest Probability *, %	Patients, n	True-Positives	True-Negatives	False-Positives	False-Negatives	Sensitivity, (95% CI), %	Specificity, (95% CI), %
Stress testing									
Overall	53	52 (50-55)	517	216	187	54	60	78 (73-83)	77 (72-83)
First Period: referred for ICA	77	63 (60-67)	181	181	31	38	47	79 (73-84)	45 (33-57)
Second Period									
Total	22	38 (34-41)	220	35	156	16	13	73 (58-64)	91 (85-94)
Referred for ICA	61	53 (46-59)	79	35	15	16	13	73 (58-84)	48 (31-67)
Not referred for ICA	0	29 (25-33)	141	0	141	0	0	NA	100 (97-100)
Total	24	38 (34-41)	220	35	152	16	17	67 (53-79)	90 (85-94)
CTCA									
Overall	53	52 (50-55)	517	274	215	26	2	99 (97-100)	89 (84-93)
First Period: referred for ICA	77	63 (60-67)	181	227	50	19	1	100 (97-100)	73 (60-82)
Second Period									
Total	22	38 (34-41)	220	47	165	7	1	98 (88-100)	96 (92-98)
Referred for ICA	61	53 (46-59)	79	47	24	7	1	98 (88-100)	77 (58-90)
Not referred for ICA	0	29 (25-33)	141	0	141	0	0	NA	100 (97-100)
Total†	24	38 (34-41)	220	47	161	7	5	91 (78-96)	96 (91-98)

CTCA = computed tomography coronary angiography; ICA = invasive coronary angiography; NA = not assessable.

* On the basis of Duke clinical score.

† Additional analysis in which we assumed that 3% of the patients with true-negative results were misclassified and actually had false-negative results.

Appendix Table 3. Distribution of Nonreferral ICA, exercise ECG and SPECT at Different Thresholds for Low, Intermediate, and High Pretest Probabilities.

Pretest Probability Threshold	Patients, n	Equivocal Exercise ECG Results, n (%)	Underwent SPECT, n (%)	Not referred for ICA, n (%)
Overall	517	76 (15)	61 (12)	141 (27)
Low				
<10%	54	7 (13)	6 (11)	32 (59)
<20%	122	13 (11)	20 (16)	67 (55)
<30%	175	18 (10)	16 (9)	90 (51)
Intermediate				
10-90%	378	54 (14)	42 (11)	106 (28)
20-80%	249	37 (15)	28 (11)	67 (27)
30-70%	162	28 (17)	16 (10)	42 (26)
High				
>90%	85	15 (18)	13 (15)	3 (4)
>80%	146	26 (18)	21 (14)	7 (5)
>70%	180	30 (17)	29 (16)	9 (5)

ECG = electrocardiography; ICA = invasive coronary angiography; SPECT = single-photon emission computed tomography

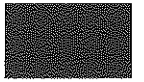
Appendix Table 4. Diagnostic Performance and Predictive Value of Stress Testing and CTCA for Detecting Coronary Artery Disease (Patient-by-Patient analysis), Using Different Thresholds for Low, Intermediate, and High Pretest Probabilities.

Test and Pretest Probability Threshold	Prevalence, % *	Pretest Probability †, %	Patients, n	True-Positives	True Negatives	False-Positives	False Negatives	Sensitivity, (95% CI), %	Specificity, (95% CI), %	PPV, (95% CI), %	NPV, (95% CI), %	+LR	-LR
Stress test													
Overall	53	52	517	216	187	54	60	78 (73-83)	77 (72-83)	80 (75-85)	76 (70-81)	3.49	0.28
Low													
<10%	19	5	54	6	34	10	4	60 (27-86)	77 (62-88)	38 (16-64)	90 (74)	2.64	0.52
<20%	20	11	122	17	81	17	7	71 (49-87)	83 (76-89)	50 (33-67)	92 (84-97)	4.08	0.35
<30%	22	15	175	30	111	25	9	77 (60-88)	82 (74-88)	55 (41-68)	93 (86-96)	4.18	0.28
Intermediate													
10-90%	51	50	378	153	146	41	38	80 (74-85)	78 (71-84)	79 (72-84)	79 (73-85)	3.65	0.26
20-80%	53	50	249	104	91	27	27	79 (71-86)	77 (68-84)	79 (71-86)	77 (68-84)	3.46	0.30
30-70%	56	53	162	72	57	15	18	80 (70-87)	79 (68-88)	83 (73-90)	76 (65-85)	3.84	0.25
High													
>90%	88	94	85	57	7	3	18	76 (65-85)	70 (35-92)	95 (85-99)	28 (13-56)	2.53	0.34
>80%	83	91	146	95	15	10	26	79 (70-89)	60 (39-78)	91 (83-95)	37 (23-53)	1.96	0.36
>70%	82	88	180	114	19	14	33	78 (70-83)	58 (39-74)	89 (82-94)	37 (24-51)	1.83	0.39
CTCA													
Overall	53	52	517	274	215	26	2	99 (97-100)	89 (84-93)	91 (87-94)	99 (96-100)	9.20	0.01
Low													
<10%	19	5	54	10	41	3	0	100 (66-100)	93 (80-98)	77 (46-94)	100 (89-100)	14.66	0.00
<20%	20	11	122	24	87	11	0	100 (83-100)	89 (80-94)	69 (50-83)	100 (95-100)	8.91	0.00
<30%	22	15	175	39	124	12	0	100 (89-100)	91 (85-91)	77 (62-88)	100 (96-100)	11.33	0.00
Intermediate													
10-90%	51	50	378	189	166	21	2	98 (96-100)	89 (83-93)	90 (85-94)	99 (95-100)	8.81	0.01
20-80%	53	50	249	130	110	8	1	99 (95-100)	93 (87-97)	94 (89-97)	99 (94-100)	14.64	0.01
30-70%	56	53	162	89	67	5	1	99 (93-100)	93 (84-97)	95 (88-98)	99 (91-100)	14.24	0.01
High													
>90%	88	94	85	75	8	2	0	100 (94-100)	80 (44-96)	97 (90-100)	100 (60-100)	5.00	0.00
>80%	83	91	146	120	18	7	1	99 (95-100)	72 (50-87)	95 (89-98)	95 (72-100)	3.54	0.01
>70%	82	88	180	146	24	9	1	99 (96-100)	73 (54-86)	94 (89-97)	96 (77-100)	3.64	0.01

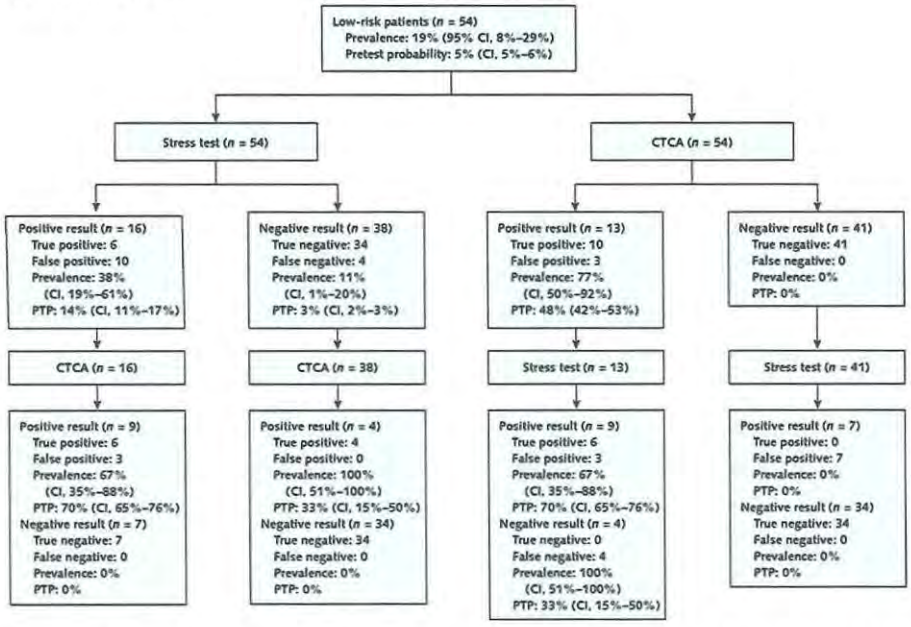
CTCA = computed tomography coronary angiography.

* Patients with coronary artery disease of those tested. For example, 24 of the 122 patients who underwent CTCA had a low pretest probability (<20%), for a prevalence of 19.7% or 20%.

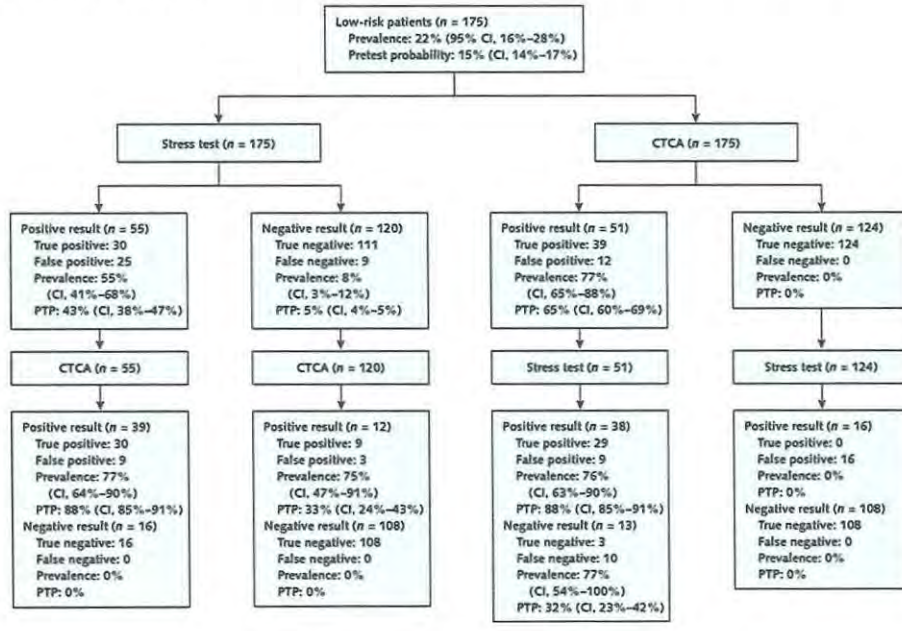
† On the basis of Duke clinical score.



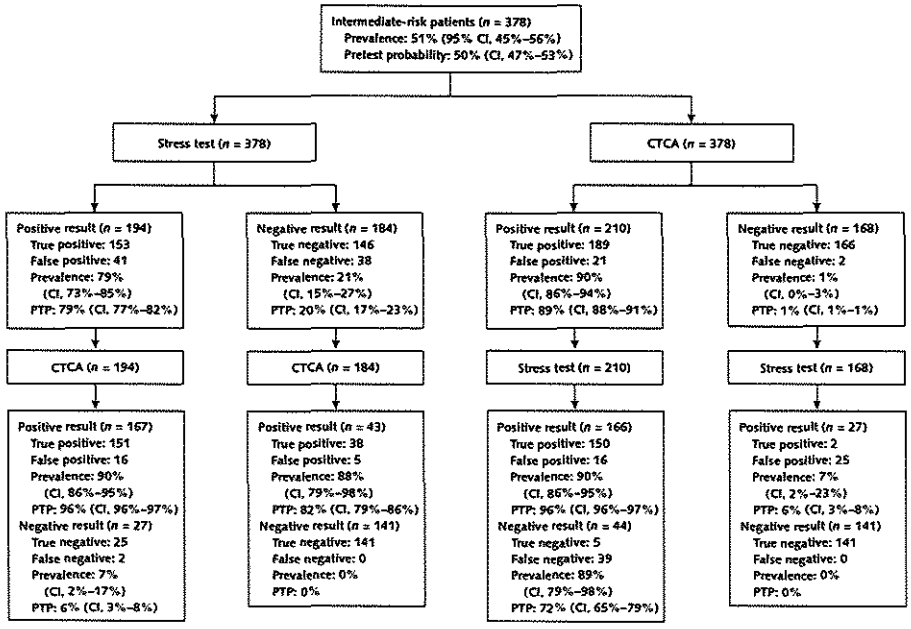
Appendix Figure 1. Intention-to-diagnose Strategies in Patients with a Low Pretest Probability less than 10%.



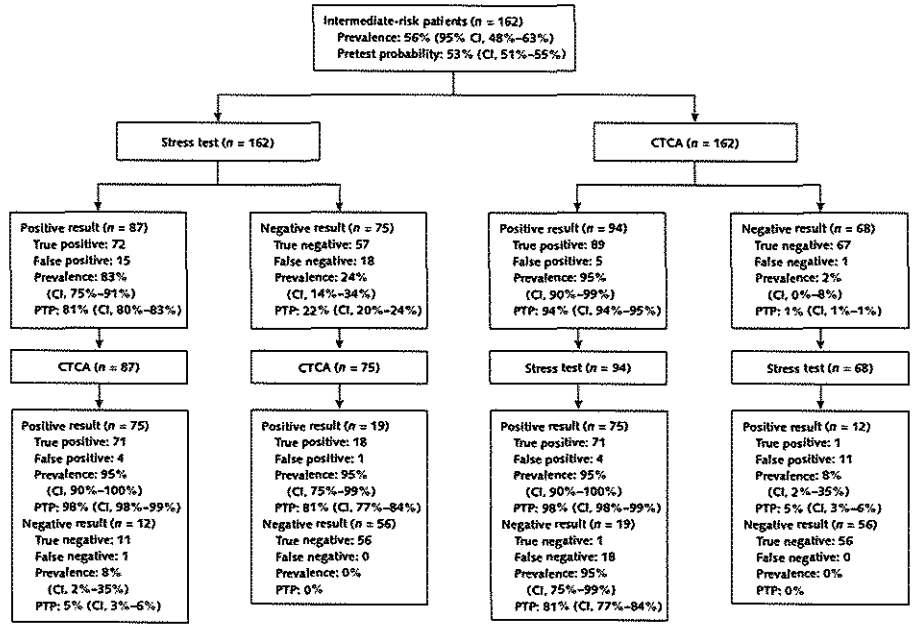
Appendix Figure 2. Intention-to-diagnose Strategies in Patients with a Low pretest Probability less than 30%.



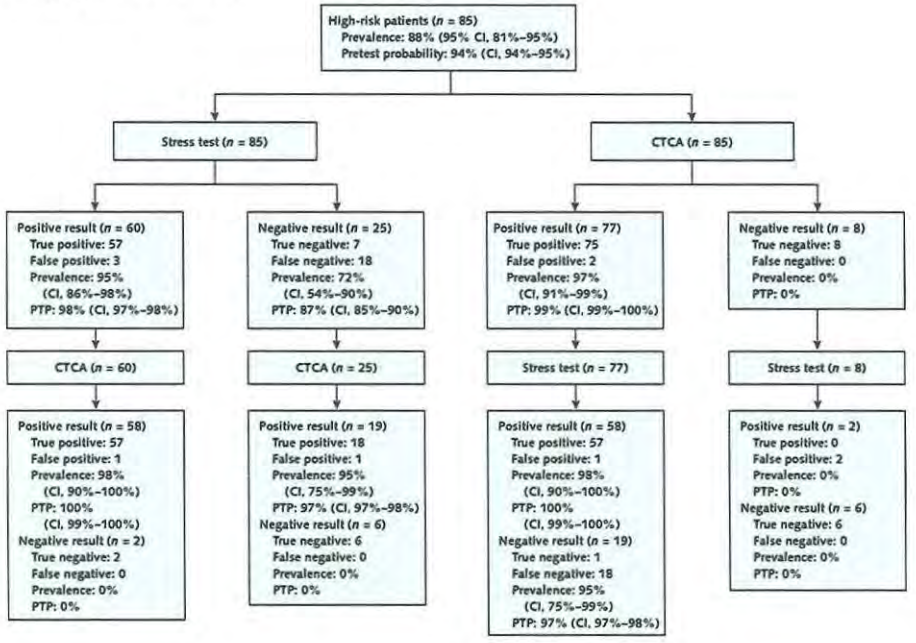
Appendix Figure 3. Intention-to-diagnose Strategies in Patients with an Intermediate Pretest Probability of 10%-90%.



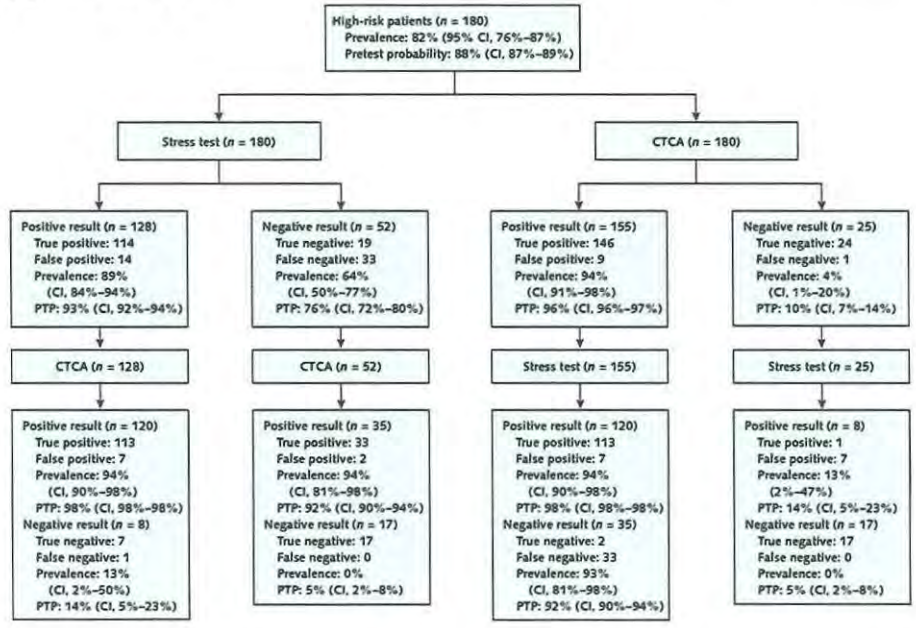
Appendix Figure 4. Intention-to-diagnose Strategies in Patients with an Intermediate Pretest Probability of 30%-70%.



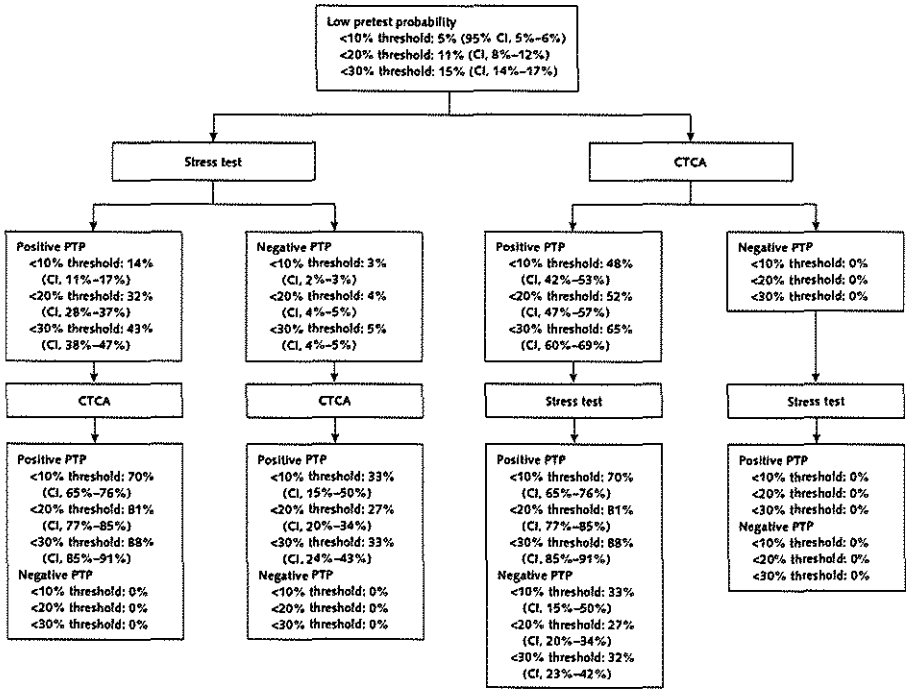
Appendix Figure 5. Intention-to-diagnose Strategies in Patients with a High Pretest Probability greater than 90%.



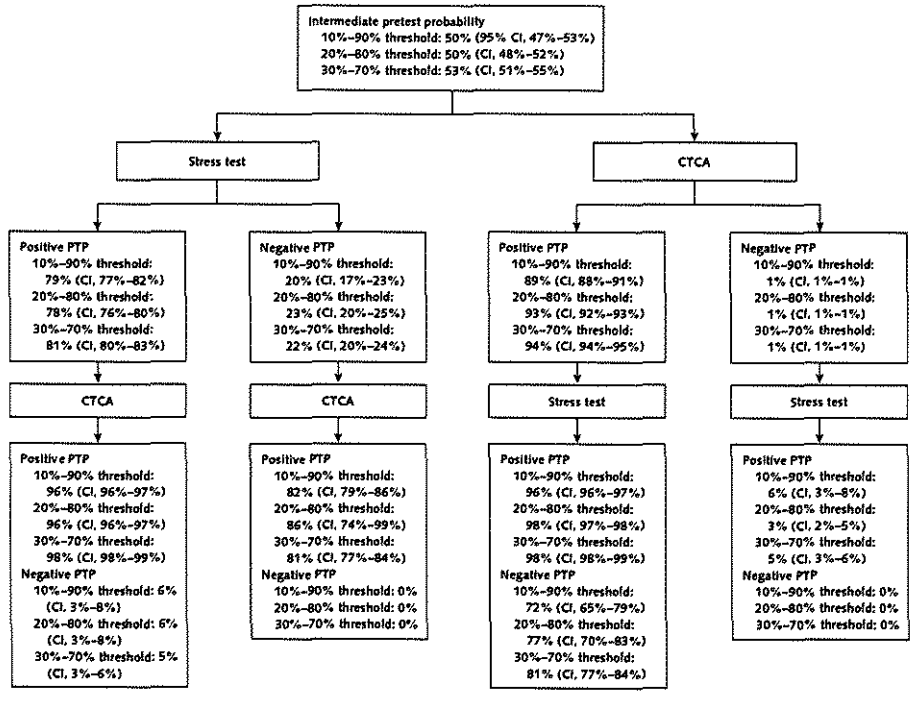
Appendix Figure 6. Intention-to-diagnose Strategies in Patients with a High Pretest Probability greater than 70%.



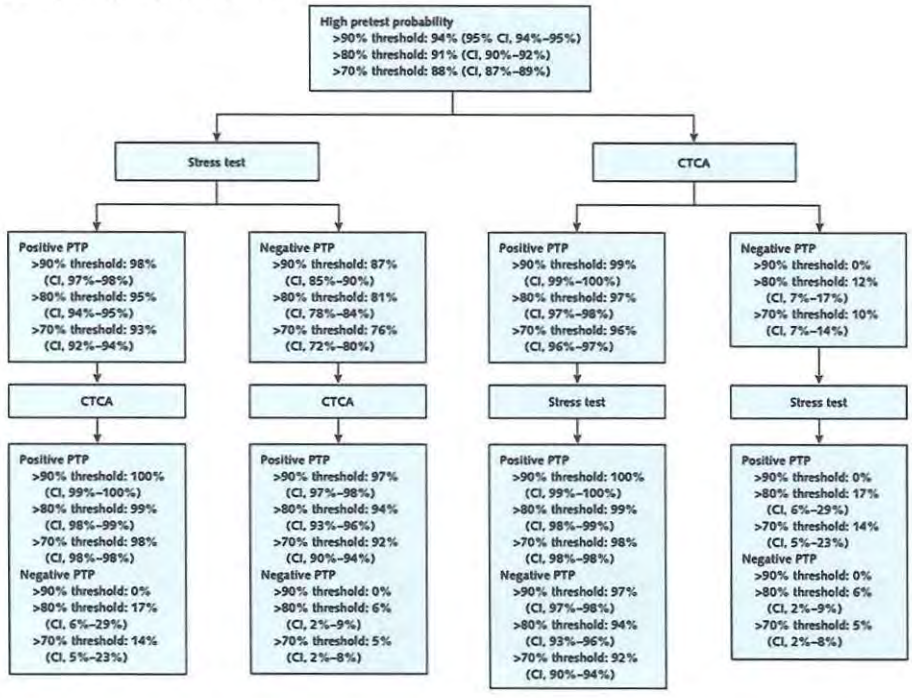
Appendix Figure 7. Intention-to-diagnose Strategy: Comparison of Low-probability Thresholds (<10%, <20%, and <30%).



Appendix Figure 8. Intention-to-diagnose Strategy: Comparison of Intermediate-probability Thresholds (10% to 90%, 20% to 80%, and 30% to 70%).



Appendix Figure 9. Intention-to-diagnose Strategy: Comparison of High-probability Thresholds (>90%, >80%, and >70%).



CHAPTER 8

A CLINICAL PROBABILITY SCORE FOR RESTRICTIVE REFERRAL TO CT CORONARY ANGIOGRAPHY

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ABSTRACT

INTRODUCTION: Restricted referral to CT coronary angiography (CTCA) of stable patients with intermediate probability of a positive CTCA, expected to have the highest diagnostic yield, may reduce the rapidly growing number of CT-scans.

OBJECTIVES: To investigate the incremental value of clinical evaluation, bicycle stress testing and CT-coronary calcium score (CCS) for the noninvasive CTCA diagnosis of obstructive coronary artery disease (CAD).To develop a clinical probability score for restrictive referral of stable patients with intermediate probability of a positive CTCA.

DESIGN: Development and validation of a three-step multivariate logistic regression model based upon clinical evaluation, bicycle testing and CCS.

SETTING: University medical center in Rotterdam, The Netherlands.

PARTICIPANTS: 543 patients with stable angina underwent clinical evaluation, bicycle testing, CCS and CTCA.

MAIN OUTCOME MEASURES: End-point was a positive CTCA (≥50% lumen diameter reduction). The discriminative power of the model was calculated by area under the receiver operator curves (AUC). The model was independently validated and calibration was tested with Hosmer-Lemeshow statistics. The reclassification of patients with intermediate probability (20% to 80%) of a positive CTCA based on this three-step multivariate logistic regression model was calculated. A clinical probability score was derived from the model with the highest discrimination by assigning numerical values to each of the significant variables according to ln (odds ratios) [OR].

RESULTS: The model including variables from clinical evaluation, bicycle testing and CCS demonstrated the highest discriminative power (AUC: 93% (95% CI: 90%-96%). Six additional variables were independently associated with a positive CTCA: high cholesterol (OR 2.3), typical angina (OR 2.6), diabetes (OR 5.7), intermediate CCS (OR 6.1), positive bicycle test (OR 9.4), and high CCS (OR 65.4). The discriminative power of the model was reproducible in the validation cohort (AUC: 94% (95% CI: 92%-96%) and the calibration was satisfactory(P = 0.465). The proportion of patients reclassified at intermediate probability of a positive CTCA could be substantially reduced with 74% (from 543 to 139). A clinical probability score of 2-5 points indicated intermediate probability (20%-80%) of CTCA diagnosis of obstructive CAD.

CONCLUSIONS: Clinical evaluation, bicycle stress testing and CCS have incremental value for noninvasive CTCA diagnosis of obstructive CAD in stable patients. A clinical probability score accurately identifies patients at intermediate probability that may benefit from CTCA and may substantially reduce the number of CTCAs that yield no useful information for clinical decision making.

INTRODUCTION

Traditionally, stress testing has been used as the initial diagnostic test in patients presenting with stable angina suspicious of obstructive coronary artery disease (CAD) [1,2]. The use of non-invasive CT coronary angiography (CTCA) has grown rapidly because of its compelling images and its revealing direct evidence of extent, location, and severity of obstructive lesions rather than the indirect evidence of stress induced ischemia tests. It should be realized, however, that CTCA should not be used indiscriminately because it is associated with radiation exposure, contrast use and considerable costs. Ideally, CTCA should therefore be used only in patients in whom CAD cannot reliably confirmed or excluded on the basis of clinical characteristics or stress testing [3,4]. There is growing evidence that CTCA is only indicated in patients with intermediate pretest probability of CAD where CTCA is useful for clinical decision making [5-7]. This requires effective risk stratification, where CTCA would not provide additional useful clinical information in patients with a low or high pretest probability of CAD.

The original approach to risk stratification as an aid in the clinical diagnosis of CAD was published by Diamond and Forrester in 1979 [8]. They estimated the pretest probability of CAD defined by age, sex and type of chest pain. The usefulness of probability analysis was correlated with the prevalence of obstructive CAD as demonstrated by autopsy or invasive coronary angiography (ICA) [8]. The majority of patients demonstrated typical angina indicating a high probability of ICA diagnosis of obstructive CAD in the population under investigation.

To date, prediction rules for CTCA diagnosis of obstructive CAD are lacking. Clinical evaluation, stress testing and CT-coronary calcium score (CCS) have shown to be useful in determining the probability of CAD prior to CTCA [9,10], but the incremental value is largely unknown. We investigated the incremental value of clinical evaluation, bicycle stress testing and CCS for the noninvasive CTCA diagnosis of obstructive CAD using a three-step multivariate logistic regression model. From the model with the highest discriminatory power, we derived a clinical probability score that allows restrictive referral to CTCA of patients with intermediate probability of a positive CTCA.

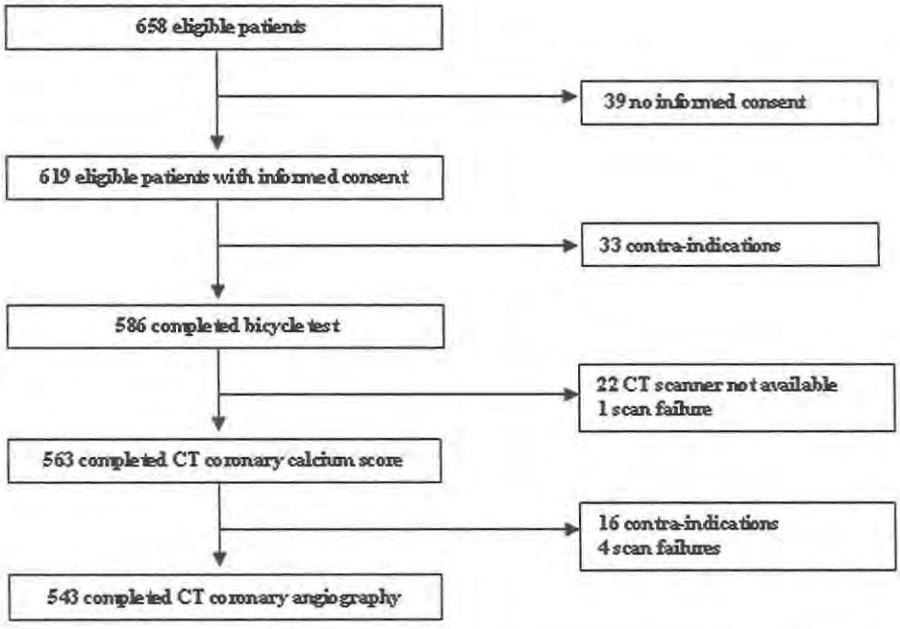
METHODS

STUDY DESIGN AND PARTICIPANTS

543 patients with stable angina suspicious for obstructive CAD underwent clinical evaluation, bicycle testing, CCS and CTCA (Figure 1). Patients were excluded from the study if they had acute coronary syndromes, previous history of percutanous coronary stent placement, coronary artery bypass surgery and prior myocardial infarction.

The study protocol was approved by our institutional review board. Patients were informed about the radiation exposure, intravenous administration of iodinated contrast medium and

Figure 1. Flow chart



potential complications (e.g. occurrence of contrast extravasation) associated with CTCA. Informed consent was obtained in all patients.

Clinical Evaluation

Patients underwent clinical evaluation by their referring physicians. Typical angina was defined when the following three characteristics were present: 1) sub-sternal discomfort 2) precipitated by physical exertion or emotion and 3) relieved with rest or nitroglycerine within 10 minutes. Atypical angina pectoris was defined when two out of these three symptom characteristics were met. Nonanginal chest pain was defined when one or none of these symptom characteristics were met. Cardiovascular risk factors associated with CAD were evaluated: hypertension (blood pressure 140/90 mm Hg or treatment for hypertension), high cholesterol (total cholesterol >180 mg/dl or treatment for high cholesterol), diabetes mellitus (treatment with oral antidiabetic medication or insulin), smoking, family history of CAD (first- or second-degree relatives with premature CAD [age<55 years]), obesity (Body Mass Index (BMI) >30 kg/m^2).

Bicycle Testing

Patients underwent bicycle testing if they had adequate exercise capacity and no contraindications (left bundle branch block, paced rhythm, Wolff-Parkinson-White syndrome, left ventricle hypertrophy, electrolyte imbalance, intraventricular conduction abnormalities, use of digitalis, aortic stenoses) 1.The test was considered positive if the electrocardiogram showed horizontal or down-sloping ST-segment depression (≥ 1mm); equivocal if ischemic ST depression was

absent but heart rate did not reach 85% of the maximum predicted for age and gender; and negative otherwise. We classified patients with equivocal bicycle test result as having a positive test result.

CT Coronary Calcium Score (CCS)

All patients underwent 64-slice computed tomography. A non-enhanced CT-coronary calcium score scan was performed prior to CTCA. Total calcium scores were calculated using dedicated software (Syngo Calcium Scoring ®, Siemens, Forchheim, Germany) and expressed as Agatston scores. Negative CCS was defined as Agatston 0. Intermediate CCS was defined as Agatston 1-400. High CCS was defined as Agatston >400.

CT Coronary Angiography (CTCA)

Patients underwent CTCA as previously described [7 11]. Patients were eligible for CTCA if they were not pregnant and had no known allergy to iodine contrast media, normal renal function (serum creatinine < 120 μmol/l), and regular heart rhythms.

For CTCA interpretation, two readers analyzed coronary segments using a modified 17-segment American Heart Association classification [12]. Segments were scored as having obstructive CAD if there was ≥50% diameter reduction of the lumen by visual assessment. Segments distal to a chronic total occlusion were excluded. All CT scans including all vessels and segments were analyzed even if the image quality was poor due to extensive calcification, coronary motion, or breathing artefacts. All CTCA results were interpreted by two readers (> 5 years experience) blinded to the results of all other tests. Interobserver disagreements were resolved in consensus in a joint session. A positive CTCA was the end-point for all analyses.

Statistical analysis

We used SPSS, version 12.1 (SPSS, Chicago, Illinois) for all statistical analyses. We report categorical variables as numbers and percentages and continuous variables as means (SDs). We determined inter-observer variability for the detection of significant stenoses on CTCA by kappa-statistics; intra-observer agreement was determined similarly based on the readings from 100 patients.

Model Development

For the development and validation of the multivariate logistic regression model, we randomly assigned patients to a development cohort (n=278) or validation cohort (n=265).

Univariate analysis

A total of 15 independent variables were analyzed in the development cohort with univariate logistic regression:

Clinical evaluation:

- Chest pain type: typical angina; atypical angina; nonanginal chest pain

- Cardiovascular risk factors: hypertension, high cholesterol, diabetes mellitus, smoking, family history of CAD, obesity

Bicycle testing

- Test result: positive (positive or equivocal), negative

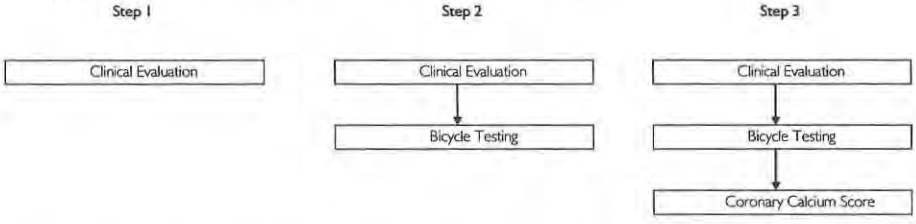
Coronary calcium score (CCS):

- Test result: negative, intermediate,high score

MULTIVARIATE ANALYSIS

Variables that achieved a significance level of $p < 0.20$ in the univariate analysis were then selected to enter the multivariate backward step-wise logistic regression to develop a three-step model (Figure 2). Step 1 comprised assessment by clinical evaluation. Step 2 comprised assessment by clinical evaluation and bicycle testing. Step 3 comprised assessment by clinical evaluation, bicycle testing and CCS. A p-value of <0.05 was required for retention in the multivariate model. Clinically relevant variables with $p > 0.05$ were forced in to the model.

Figure 2. Three-step multivariate logistic regression model



For each step of the model, the probability of a positive CTCA was calculated (Appendix A). For each step, the area under the receiver operator curve (AUC) was calculated to assess the discriminatory power of the model.

MODEL VALIDATION

The validation cohort was used to validate the previously developed multivariate model. For each step, the AUC was calculated to validate the discriminatory capacity of the model.

Calibration, that is, agreement between predicted and observed probabilities, was tested with the Hosmer-Lemeshow goodness-of-fit-test [13].

Patient Reclassification

For each step, the proportion of patients reclassified to low, (<20%), intermediate, (20-80%) and high probablity (>80%) of a positive CTCA was calculated in the total study population.

We altered the threshold of intermediate probability (10% to 90%; and 30% to 70%) to test sensitivity of our findings to these primary thresholds.

Clinical Probability Score

A clinical probability score was derived from the multivariate model with the highest discrimination. Each independent variable was assigned a weighted numerical value according to ln (odds ratios) [OR]. The total score was generated by summing the numerical values (Appendix B).

Table 1. Baseline Clinical Characteristics (n= 543)

Parameter	Development Cohort (n=278)	Validation Cohort (n=265)	P-value
Mean age (SD), y	58.4 (10.4)	58.4 (10.0)	0.978
Male, %	179 (64)	152 (57)	0.093
Risk factors, n (%)			
Hypertension	128 (46)	122 (46)	0.999
High cholesterol	134 (48)	132 (50)	0.708
Diabetes mellitus	42 (15)	34 (13)	0.444
Smoker	64 (23)	64 (24)	0.757
Family history of coronart artery disease	150 (54)	134 (51)	0.429
Obesity	43 (15)	36 (14)	0.571
Chest pain, n (%)			
Typical angina	108 (39)	109 (41)	0.562
Atypical angina	69 (25)	64 (25)	0.876
Nonanginal chest pain	101 (36)	91 (34)	0.651
Bicycle test			
Positive test	131 (47)	122 (46)	0.8
Coronary Calcium Score (CCS)			
Negative CCS (0)	91 (33)	85 (32)	0.728
Intermediate CCS (1-400)	116 (42)	114 (43)	0.896
High CCS (>400)	64 (23)	63 (24)	0.907
CT Coronary Angiography (CTCA)			
Positive test	147 (53)	139 (52)	0.921

RESULTS

The baseline characteristics of the development and validation cohorts are presented in Table 1. The overall prevalence of obstructive disease at CTCA was 53% (286/543). There were no significant differences ($p > 0.05$) observed among the cohorts. Observer variability for detection of significant stenoses by CTCA was good (interobserver κ, 0.90 [95% CI, 86 to 94]; intraobserver κ, 0.98 [CI, 94 to 100]).

MODEL DEVELOPMENT

UNIVARIATE ANALYSIS

Of the 15 variables evaluated, 11 remained statistically significant in the univariate analysis (Table 2). Variables independently and strongly (OR >5.0) associated with a positive CTCA were typical angina, positive bicycle test and high CCS.

MULTIVARIATE ANALYSIS

STEP 1: Six variables remained statistically significant in the multivariate analysis (Table 3).

Patients with typical angina were significantly most likely to have a positive CTCA (OR 3.5). The other variables independently associated with a positive CTCA were age, gender, smoking, high cholesterol, and diabetes mellitus.

STEP 2: Six variables remained statistically significant in the multivariate analysis (Table 3). Patients with a positive bicycle result were significantly most likely to have a positive CTCA (OR 10.8). The other variables independently associated with a positive CTCA were diabetes mellitus, typical angina, gender, high cholesterol, and age. The variable male ($p = 0.083$) was forced into the model.

Table 2. Development: Univariate Analysis - Independent Variables (p-value < 0.20).

Development cohort (n=278) Independent Variables	Odds Ratio [OR]	95% CI	p -Value
Negative CCS	0.1	0.0-0.1	<0.001
Nonanginal chest pain	0.3	0.2-0.4	<0.001
Age per year	1.1	1.1-1.1	<0.001
Smoker	1.7	0.9-3.0	0.080
Hypertension	1.8	1.1-3.0	0.013
Male	1.9	1.2-3.2	0.010
Diabetes mellitus	3.4	1.6-7.2	0.002
High cholesterol	3.6	2.2-5.8	<0.001
Typical angina	5.1	3.0-8.7	<0.001
Positive bicycle test	13.0	7.3-23.2	<0.001
High CCS	31.6	9.6-104.2	<0.001

STEP 3: Six variables remained statistically significant in the multivariate analysis (Table 3). Patients with a high CCS were significantly most likely to have a positive CTCA (OR 65.4). The other variables independently associated with a positive CTCA were a positive bicycle test, intermediate CCS score, diabetes mellitus, typical angina and high cholesterol.

Table 3. Model Development: Multivariate Analysis - Independent Variables (p-value <0.05).

Development cohort (n=278) Multivariat model	Independent Variables	Odds Ratio [OR]	95% CI	p -Value
Step 1	Age per year	1.1	1.0-1.1	0.001
	Gender	2.2	1.2-4.0	0.013
	Smoking	2.2	1.1-4.5	0.025
	High cholesterol	2.8	1.6-5.0	0.001
	Diabetes mellitus	3.1	1.3-7.3	0.009
	Typical angina	3.5	1.9-6.4	<0.001
Step 2	Age per year	1.1	1.0-1.1	0.001
	Male	1.8	0.9-3.6	0.083
	Typical angina	2.6	1.3-5.3	0.008
	High cholesterol	2.6	1.4-5.1	0.004
	Diabetes mellitus	4.2	1.6-10.9	0.003
	Positive bicycle test	10.8	5.5-21.2	<0.001
Step 3	High cholesterol	2.3	1.1-4.7	0.029
	Typical angina	2.6	1.2-5.7	0.018
	Diabetes mellitus	5.7	1.8-18.3	0.004
	Intermediate CCS	6.2	2.7-14.1	<0.001
	Positive bicycle test	9.5	4.5-20.2	<0.001
	High CCS	65.4	15.6-275.1	<0.001

Table 4. Model Development and Validation: Multivariate Analysis - Discriminatory Capacity

Multivariate model	Development cohort (n=278) Area-under-Curve (%)	Validation cohort (n=265) Area-under-Curve (%)
Step 1	82.2 (77.3-87.0)	80.8 (77.2-84.4)
Step 2	88.9 (85.0- 92.7)	90.8 (88.2-93.3)
Step 3	92.7 (89.5-95.9)	93.6 (91.5-95.7)

The AUC and the formulas used to calculate the probabilities of a positive CTCA for each step are presented in Table 4. Step 1 demonstrated AUC of 82%; step 2 significantly increased AUC to 89% and step 3 significantly further increased AUC to 93%.

Model Validation

There were no significant ($p < 0.05$) differences in AUC for step 1 (81%), step 2 (91%) and step 3 (94%) (Table 4). The calibration of model variables was satisfactory without clear evidence for poor fit for each model (step 1: $p = 0.765$; step 2: $p = 0.392$; step 3: $p = 0.465$).

Patient Reclassification

1. Intermediate probability of a positive CTCA: threshold from 20% to 80%

Step 1, 2 and 3 reduced the initial number of patients remaining in the intermediate probability group with 39% (from 543 to 332), with 61% (from 543 to 210) and with 74% (from 543 to 139), respectively (Figure 3).

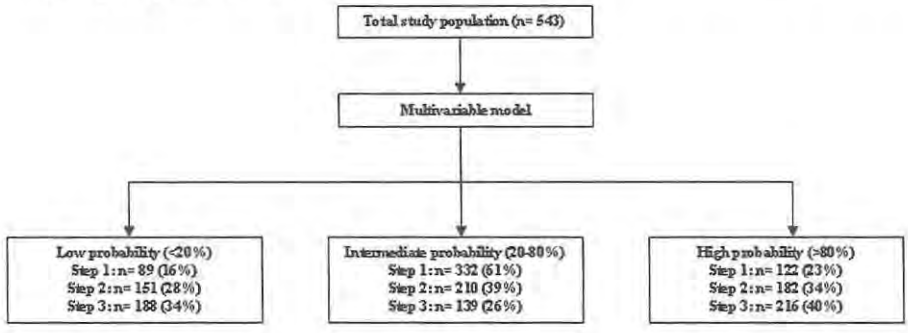
2. Intermediate probability of a positive CTCA: threshold from 10% to 90%

Step 1, 2 and 3 reduced the initial number of patients remaining in the intermediate probability group with 15% (from 543 to 464), with 35% (from 543 to 355) and with 50% (from 543 to 269), respectively (Appendix Figure 1).

3. Intermediate probability of a positive CTCA: threshold from 30% to 70%

Step 1, 2 and 3 reduced the initial number of patients remaining in the intermediate probability group with 60% (from 543 to 215), with 77% (from 543 to 125) and with 80% (from 543 to 110), respectively (Appendix Figure 2).

Figure 3. Patient Classification in Low (<20%), Intermediate (20-80%) and High (>80%) Probability of a positive CTCA



CLINICAL PROBABILITY SCORE

A clinical probability score was derived from the multivariate model using independent variables from clinical evaluation, bicycle testing and CCS (step 3). The relation between between calculated probability by the multivariate model (step 3) and the clinical probability score is presented (Figure 4A).

1. INTERMEDIATE PROBABILITY OF A POSITIVE CTCA: THRESHOLD FROM 20% TO 80%

A score of 0-2 [exact: 0-2.3] was associated with low (<20%) probability of having a positive CTCA, whereas a score of 2-5 [exact: 2.3-4.9] was associated with intermediate (20-80%) probability. A score of 5-10 [exact: 4.9-9.9] was associated with high (>80%) probability (Figure 4B).

2. INTERMEDIATE PROBABILITY OF A POSITIVE CTCA: THRESHOLD FROM 10% TO 90%

A score of 0-2 [exact: 0-1.7] was associated with low (<10%) probability of having a positive CTCA, whereas a score of 2-6 [exact: 1.7-5.8] was associated with intermediate (10-90%) probability. A score of 6-10 [exact: 5.8-9.9] was associated with high (>90%) probability (Appendix Figure 3).

3. INTERMEDIATE PROBABILITY OF A POSITIVE CTCA: THRESHOLD FROM 30% TO 70%

A score of 0-3 [exact: 0-2.6] was associated with low (<30%) probability of having a positive CTCA, whereas a score of 3-4 [exact: 2.6-4.4] was associated with intermediate (30-70%) probability. A score of 4-10 [exact: 4.4-9.9] was associated with high (>70%) probability (Appendix Figure 4).

A practical calculator for the clinical probability score is presented (Figure 5).

DISCUSSION

The number of CTCAs is increasingly growing for diagnosis of obstructive CAD in symptomatic stable patients [14]. The very high negative predictive value (>95%) strongly supports the use of CTCA as reliable gatekeeper to invasive coronary angiography, in particular, in patients with intermediate probability of CAD [5-7]. However, CTCA is associated with radiation exposure to the patient and if applied inappropriately may increase costs.

We demonstrated that clinical evaluation, bicycle stress testing and CCS have incremental value for CTCA diagnosis of obstructive CAD in stable patients.

Figure 4A. Relation between Calculated Probability of CTCA diagnosis of obstructive CAD (based on multivariate model Step 3) and Clinical Probability Score.

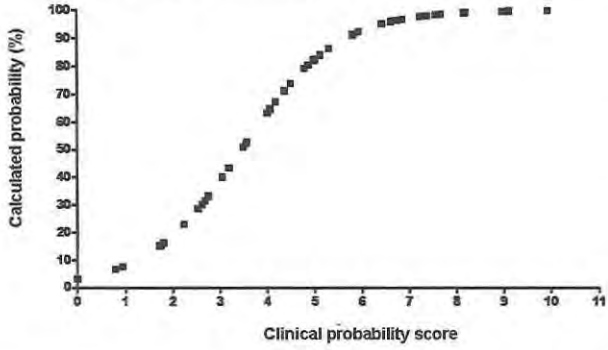
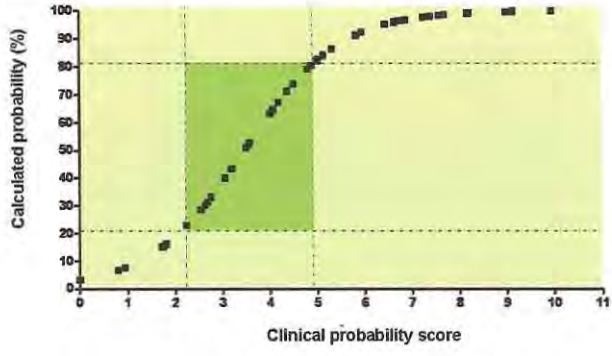


Figure 4B. Relation between Calculated Intermediate (from 20% to 80%) Probability of CTCA diagnosis of obstructive CAD and Clinical Probability Score [2-5 points; exact 2.3-4.9] (dark green box).



The presence of coronary calcium is a strong marker of coronary atherosclerosis 15 and there is a direct relation between the magnitude of CCS and the presence of a coronary obstruction 16 17. However, there is only limited data on the diagnostic utility of CCS in patients with stable angina. The interpretation of CCS alone results in a large number of false-positive findings with notably low diagnostic specificity [18].

The three-step multivariate logistic regression model showed that the traditionally used clinical evaluation, a combination of age, gender, and risk factors (step 1), predicted a CTCA diagnosis of obstructive CAD with AUC of 82%, addition of bicycle testing further significantly increased predictive power to AUC of 89% (step 2), and final addition of the CCS (step 3) again significantly increased predictive power to AUC of 93%. We further demonstrated that a high reproducibiliy and calibration was achieved after validation of this multivariate model in another randominlgy assigned cohort with similar demographic characteristics.

In our study we assumed that CTCA provides useful additional information only in patients who could be classified as having intermediate probability of CTCA diagnosis of obstructive CAD. Classification to low, intermediate or high probability categories is only clinically meaningful if this classification does not negatively affect patient safety and is associated with significant difference in patient management in each category.We assumed that patients classified to a low probability category of CTCA diagnosis of obstructive disease, in the majority having non-anginal chest pain, negative bicycle test and negative calcium score, do not require further testing by CTCA and can be safely discharged because these patients have an excellent prognosis [19 20].

Figure 5. Clinical Probability Score: A practical calculator

	Points
High cholesterol	1.0
Typical angina	1.0
Diabetes mellitus	1.5
Intermediate coronary calcium score (Agatston 1-400)	2.0
Positive bicycle test	2.5
High coronary calcium score (Agatston >400)	+ 4.0
Total score	.....

Patients classified to a high probability category of CTCA diagnosis of obstructive disease, in the majority having typical angina, a positive bicycle test and a positive calcium score, should not be referred to CTCA but may require direct referral to invasive coronary angiography to assess suitability for medical treatment or revascularization. However an additional functional test such as SPECT or stress echocardiography to assess the presence and severity of myocardial ischemia may also provide useful diagnostic information because patients with no or mild ischemia require optimal medical treatment and those with moderate to severe iaschemia fare better with coronary revascularization [21-23]. CTCA in this high probability category is less appropriate because, in particular in intermediate lesions, invasive fractional flow reserve measurements over- or underestimates the flow limiting effects of CTCA detected coronary lesions [24].

The clinical probability score, derived from the model with the highest discrimation, may serve as an efficient and accurate indicator for restrictive referral to CTCA only in patients with stable angina and intermediate probability of CTCA diagnosis of obstructive CAD. The score is easily obtainable using inexpensive parameters, including age, gender, presentation of chest pain, cardiovascular risk factors, and the widely available bicycle stress test, whereas CCS can be obtained by a low-dose radiation exposure, quick scan, without the need for invasive contrast administration.

LIMITATIONS

Our study was a single center study performed in a moderately large population of patients with stable angina. Larger, multi-center randomized studies are needed to confirm our initial results and whether similar results can be obtained in a less restricted patient population including those with previous myocardial infarction, or prior revascularization with PCI or CABG.

For the development and validation of the multivariate logistic regression model, we split the sample size and randomly assigned patients to a development or validation cohort. Possible biases present in the data may have been randomly allocated equally to each of the cohorts. Future studies should include external and prospective validation of the clinical probability score as presented.

A perfectly calibrated prediction model should have an AUC of only 83% [25]. However, a prediction model cannot be both perfectly reliable and perfectly discriminatory. In our model, the AUCs of step 1 (89%) and step 2 (93%) indicate that calibration (reliability) is to some extent being sacrificed for improved discrimination (patients who will have a positive CTCA and those who will not).

The avoidance of unnecessary radiation exposure is mandatory and partly underlies the goal of our study to reduce the number of patients undergoing CTCA. This was achieved by using CCS, that had incremental discriminative power to clinical evaluation and bicycle stress testing. However, like CTCA, CCS is associated with a substantially smaller but not neglectable patient dose, partly off-setting the magnitude of radiation exposure reduction.

We investigated the incremental value of clinical evaluation, bicycle testing and CCS in the noninvasive CTCA diagnosis of obstructive CAD. Since both CCS and CTCA provide anatomical information this may have favored CCS (Step 3) over bicycle testing (Step 2) in the model discriminatory strength. Nevertheless, the presence of coronary calcium is an independent marker of CAD and has not only diagnostic incremental value but is also known to have prognostic value [19].

CLINICAL IMPLICATIONS

To restrain the continuing growth of health care costs while preserving quality of care, one needs to avoid unnecessary diagnostic imaging [26]. Our study showed that it was possible to improve the efficacy of a non-invasive diagnostic strategy to detect or exclude obstructive CAD at CT coronary angiography. The application of a clinical probability score, based on clinical evaluation, bicycle stress testing and the CT-coronary calcium score can be used to safely identify symptomatic stable patients at intermediate probability who may optimally benefit from CTCA and may substantially reduce the number of CTCAs that yield no useful information for clinical decision making.

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APPENDIX

APPENDIX A. THREE-STEP MULTIVARIATE MODEL

The probability of a positive CTCA was calculated as:

$1/(1+e^{-x})$

where e = base of natural logarithm

$$x = a_1y_1 + a_2y_2 + \ldots + a_ky_k + B$$

where y_k = variables

a_k = corresponding logistic regression coefficients

B = intercept term

Predictive variables with their coefficients are listed below for each step.

STEP 1

VARIABLE	COEFFICIENT
Age per year	0.070
Male	0.773
Smoke	0.808
Diabetes	1.136
High cholesterol	1.027
Typical angina	1.241

In this step, B = -5.780.

STEP 2

VARIABLE	COEFFICIENT
Age per year	0.062
Male	0.597
Diabetes	1.442
High cholesterol	0.972
Typical angina	0.955
Positive bycicle test	2.382

In this step, B = -5.932.

STEP 3

VARIABLE	COEFFICIENT
Diabetes	1.738
High cholesterol	0.814
Typical angina	0.948
Positive bycicle test	2.249
Intermediate CCS	1.818
High CCS	4.180

In this step, B = -3.471.

APPENDIX B. CLINICAL PROBABILITY SCORE (DERIVED FROM STEP 3)

The clinical probability score was calculate as:

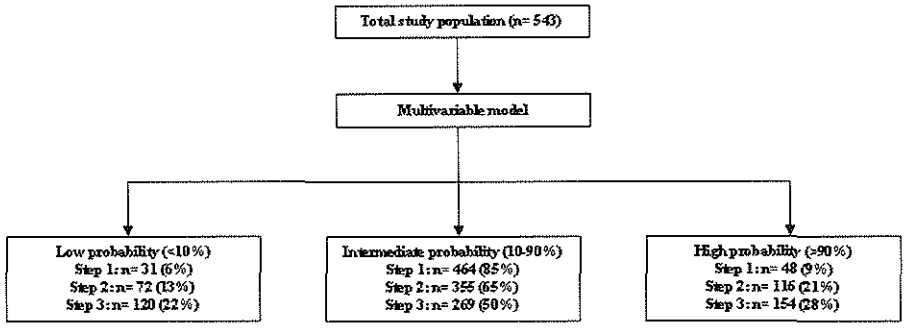
$$\text{Score} = a_1y_1 + a_2y_2 + \ldots + a_ky_k$$

where y = variable

a = corresponding logistic regression coefficient

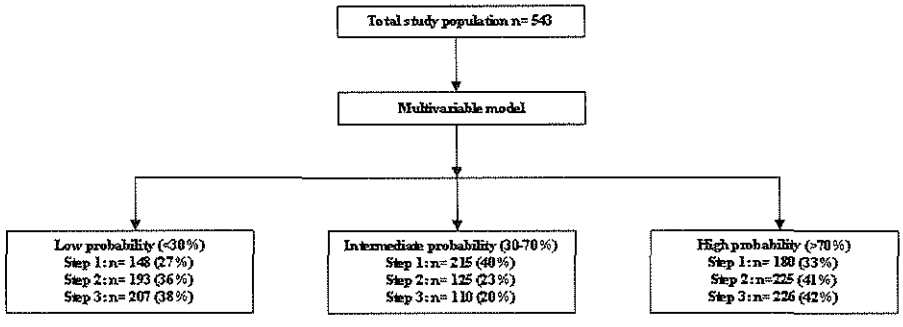
APPENDIX FIGURE 1.

Patient reclassification in low (<10%), intermediate (10-90%), and high probability (>90%) of having a CTCA diagnosis of obstructive CAD.



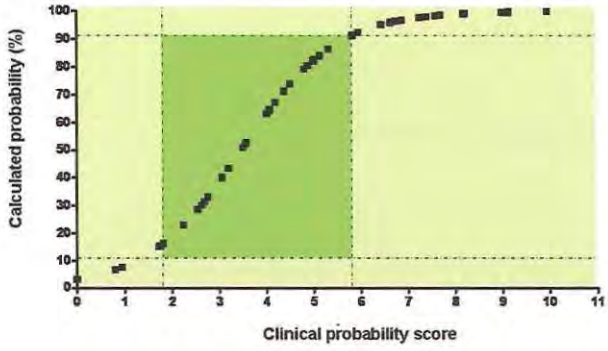
APPENDIX FIGURE 2.

Patient reclassification in low (<30%), intermediate (30-70%), and high (>70%) probability of having a CTCA diagnosis of obstructive CAD.



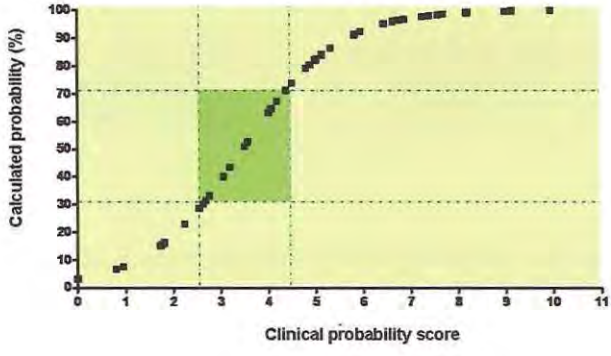
Appendix Figure 3.

Relation between Calculated Intermediate (from 10% to 90%) Probability of CTCA diagnosis of obstructive CAD and Clinical Probability Score [2-6 points exact 1.7-5.8] (dark green box).



Appendix Figure 4.

Relation between Calculated Intermediate (from 30% to 70%) Probability of CTCA diagnosis of obstructive CAD and Clinical Probability Score [3-4 points; exact 2.6-4.4] (dark green box).



PART 4

RADIATION EXPOSURE ASSOCIATED WITH CT CORONARY ANGIOGRAPHY

CHAPTER 9

OPTIMAL ELECTROCARDIOGRAPHIC PULSING WINDOWS AND HEART RATE: EFFECT ON IMAGE QUALITY AND RADIATION EXPOSURE AT DUAL-SOURCE CORONARY CT ANGIOGRAPHY

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ABSTRACT

PURPOSE: To determine the optimal width and timing of the electrocardiographic (ECG) pulsing window within the cardiac cycle in relation to heart rate (HR), image quality, and radiation exposure in patients who are suspected of having coronary artery disease.

MATERIALS AND METHODS: The institutional review board approved the study, and all patients gave informed consent. Dual-source computed tomography (CT) was performed in 301 patients (mean HR, 70.1 beats per minute ± 13.3 [standard deviation]; range, 43-112 beats per minute) by using a wide ECG pulsing window (25%-70% of the R-R interval). Data sets were reconstructed in 5% steps from 20%-75% of R-R interval. Image quality was assessed by two observers on a per-segment level and was classified as good or impaired. High-quality data sets were those in which each segment was of good quality. The width and timing of the image reconstruction window was calculated. On the basis of these findings, an optimal HR-dependent ECG pulsing protocol was designed, and the potential dose-saving effect on effective dose (in millisieverts) was calculated.

RESULTS: At low HR (≤ 65 beats per minute), high-quality data sets were obtained during end diastole (ED); at high HR (≥ 80 beats per minute), they were obtained during end systole (ES); and at intermediate HR (66-79 beats per minute), they were obtained during both ES and ED. Optimal ECG pulsing windows for low, intermediate, and high HR were at 60%-76%, 30%-77%, and 31%-47% of the R-R interval, respectively, and with these levels, the effective dose was decreased at low HR from 18.7 to 6.8 mSv, at intermediate HR from 14.7 to 13.4 mSv, and at high HR from 11.3 to 4.2 mSv.

CONCLUSION: With optimal ECG pulsing, radiation exposure to patients, particularly those with low or high HR, can be reduced with preservation of image quality.

INTRODUCTION

Coronary computed tomographic (CT) angiography has emerged as a noninvasive diagnostic modality that can reliably help exclude the presence of significant coronary artery disease (50% lumen diameter reduction) (1–8). However, the radiation exposure associated with CT scanning is high (9), as compared with conventional coronary angiography, and may result in restricted clinical use.

Technologic improvements are required to reduce radiation exposure and to preserve CT image quality. The dual-source (DS) CT scanner is equipped with two x-ray sources; this configuration results in an improved temporal resolution of 83 msec that allows scanning at higher heart rates (HRs) (10–14). The radiation exposure is reduced primarily because of the increased pitch, and thus shorter scan times, in patients with higher HR. An additional cardiac bow-tie filter and a smaller field of view with the second detector can reduce radiation exposure further (14).

In addition, DS CT is equipped with electrocardiographically triggered x-ray tube modulation, or electrocardiographic (ECG) pulsing. Prior to the scan, the operator can manually select the width and timing of the ECG pulsing window in the R-R interval during which full tube current is given. The ECG pulsing window is preferably positioned within the cardiac cycle when the heart moves less (e.g., end systole and end diastole) to obtain motion-free images of the coronary arteries. The tube current outside the pulsing window can be set at 20% (functional analysis possible) or 4% of the nominal tube current, and hence the total radiation exposure can be greatly reduced.

The aim of this study was to determine the optimal width and timing of the ECG pulsing window within the cardiac cycle in relation to HR, image quality, and radiation exposure in patients who are suspected of having coronary artery disease.

MATERIALS AND METHODS

From July 2006 to June 2007, we included 362 consecutive symptomatic patients who were suspected of having coronary artery disease and were scheduled to undergo conventional coronary angiography. Only patients who had sinus rhythm without a previous history of percutaneous intervention or bypass surgery were included. Excluded were patients with known allergy to iodinated contrast material (n = 11); patients with impaired renal function, defined by a serum creatinine value of more than 120 μmol/L (n = 18); patients with persistent arrhythmias (n = 17); or patients in whom there was a logistic inability to perform CT before conventional coronary angiography (n = 15). Thus, the study population comprised 301 patients (215 men, 86 women; mean age, 63.6 years ± 10.6 [standard deviation]; range, 25–89 years). The institutional review board approved the study, and all patients gave informed consent.

No oral or intravenous β-blockers were administered prior to scanning. All patients received nitroglycerin (0.4 mg) sublingually just before scanning. Patient age, sex, and body mass index were recorded.

All patients were scanned by using a DSCT scanner (Somatom Definition; Siemens Medical Solutions), and they had a mean HR of 70.1 ± 13.3 beats per minute, with a range of 43–112 beats per minute. The system is equipped with two x-ray tubes and two corresponding detectors mounted on a single gantry with an angular offset of 90° and a gantry rotation time of 330 msec (15). DSCT scan parameters were as follows: number of x-ray sources, two; detector collimation, with number of detector rows and section thickness of 32 x 0.6 mm, with double sampling by using rapid alteration of the focal spot in the longitudinal direction (z-axis flying focal spot); rotation time, 330 msec; and tube voltage, 120 kV. The pitch varied between 0.2 for low HRs (<40 beats per minute) and 0.53 for high HRs (>100 beats per minute), with individually adapted pitch values for HRs of more than 40 beats per minute and less than 100 beats per minute. Each tube provided a maximum of 412 mAs per rotation and full x-ray tube current (624 mA per tube was given from 25-70% of the R-R interval to include both the end-systolic (ES) and end-diastolic (ED) phases. The tube current was reduced to 20% of the maximum tube current outside the ECG pulsing window. A bolus of iodinated contrast material (Ultravist 370; Schering, Berlin, Germany), which varied between 60 and 100 mL depending on the expected scan time, was injected at a flow rate of 5.5 mL/sec in an antecubital vein, followed by a saline bolus chaser administered at a flow rate of 5.5 mL/sec. A bolus-tracking technique was applied to synchronize the data acquisition with the arrival of contrast agent in the coronary arteries.

All coronary CT angiographic data sets were reconstructed by using a single-segment reconstruction algorithm, with the following parameters: section thickness, 0.75 mm; increment, 0.4 mm; medium-to-smooth convolution kernel, B26f; and spatial resolution, 0.6–0.7 mm (in plane) and 0.5 mm (through plane) (15). Average HR, scan length (in centimeters), scan time, pitch, and contrast agent load were recorded. For each patient, 12 data sets were reconstructed in 5% steps from 20% to 75% of the R-R interval.

All images were transferred to a dedicated workstation (Multi-Modality; Siemens Medical Solutions). During a 3-month period, two observers (A.C.W. and N.R.M., with 3 and 7 years of experience in cardiovascular imaging, respectively) independently evaluated image quality on a per-segment level in all 12 data sets. The images were sequentially presented to the observers. Coronary segments were classified according to a 17-segment modified American Heart Association classification (16). Image quality was classified as (a) good, for an image with no or mild coronary motion artifact present and the observer was confident in the findings at image evaluation, or (b) impaired, for an image with extensive coronary motion artifact present and the observer experienced impairment in performing the diagnostic evaluation.

The image quality was assessed for each segment with a blood vessel diameter of at least 1.5 mm. Axial views, maximum intensity projections, and (curved) multiplanar reformations

were used to identify coronary motion artifacts. Three months after the initial evaluation, one observer (A.C.W.) reanalyzed a randomly selected set of 100 data sets to determine the intraobserver agreement. Both observers (A.C.W. and N.R.M.) independently selected the best ES and ED data sets that provided the largest number of segments with good image quality. The selected data set was defined as high quality if all segments demonstrated good image quality. Interobserver disagreements were resolved in consensus in a joint session.

Classification according to HR groups

After plotting the frequency of high-quality data sets reconstructed during ES, ED, or both ES and ED in relation to HR, patients were classified according to low, intermediate, and high HRs (Fig 1).

ECG pulsing window

For each HR group, the optimal width of the image reconstruction window during ED and ES was calculated, including exact 95% confidence intervals. The optimal timing (during ES, ED, or both ES and ED) of the ECG pulsing window was determined by evaluating the differences in occurrence of high-quality ES and ED data sets in each HR group. The optimal width of the ECG pulsing window (in percentages) corresponded to the calculated width of the image reconstruction window for each HR group.

Effective dose

The effective dose for coronary DS CT angiography was estimated, with the use of Monte Carlo estimations (ImPACT CT Patient Dosimetry Calculator, version 0.99x; St George's Healthcare NHS Trust, Tooting, London, England) that are available at impactscan.org, and was derived from CT dose index volume measurements obtained from the CT scanner console. The CT dose index volume is used to estimate the average radiation dose within the scanned volume on the basis of a standardized phantom (17).

For each HR group, the potential effect of the optimal ECG pulsing window on the effective dose was calculated by using the following equations: $Epat = (0.45 \cdot Emax) + [(0.55 \cdot Emax)/T]$ and $Eopt = (W.Emax) + [(1-W) \cdot Emax/T]$, where Epat is the effective dose that is based on the Monte Carlo estimations in each patient, Emax is the calculated dose by using maximum tube current throughout the entire cardiac cycle, Eopt is the calculated effective dose by using optimized ECG pulsing, W is the width of the optimal pulsing window, and T is the tube current outside the pulsing window as a percentage of the nominal tube current: T20% = 5 and T4% = 25.

Statistical Analysis

Statistical analysis was performed by using software (SPSS, version 12.0.1; SPSS, Chicago, Ill). Continuous variables were reported as means and standard deviations, and categorical variables were reported as frequencies or percentages. Comparison between HR groups for age and body mass index was calculated by using the analysis of variance test, and comparison between HR groups for sex was calculated by using the χ^2 test. Inter- and intraobserver variability

for the evaluation of image quality was determined by using the K-statistic. The McNemar test was used to evaluate the difference between the frequency of high-quality data sets reconstructed in ED and ES. An additional agreement analysis was performed after random selection of a single segment per data set in each patient to explore the effect of nesting.

Table 1. Percentage of Images Obtained with Good Quality on Per-Segment and Per-Patient Levels.

		N	ED, %	ES, %	ED + ES, %
Patient level		301	71	81	93
Segment level	All	4406	95	98	99
	proximal	1192	98	99	100
	mid	900	94	96	99
	distal	1089	94	97	99
	side	1225	97	99	100

N indicates number; ED, end-diastole; ES, end-systole * proximal segments included segments 1, 5, 6, and 11; mid segments, segments 2, 7, and 13; distal segments, segments 3, 4, 8, and 15; and side segments, segments 9, 10, 12, 14, 16, and 17.

RESULTS

IMAGE QUALITY

In total, 4406 coronary artery segments were evaluated (Table 1). The statistics of the inter- and intraobserver agreement for the evaluation of image quality were 0.73 and 0.81, respectively. The agreement analysis in which the effect of the clustered nature of the data was explored demonstrated practically identical statistics (0.75), which indicated that there was a negligible correlation between observations within each patient.

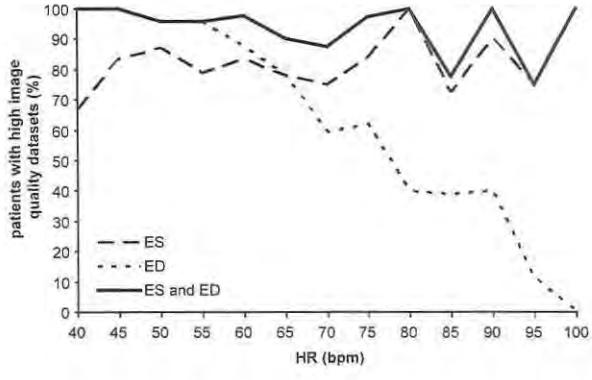


Figure 1. Distribution of High Quality End-Systolic (ES) and End-Diastolic (ED) Datasets in Relation to Heart Rate.

A high-quality data set was found during ES in 81% (n = 244) of 301 patients and during ED in 71% (n = 214) of those patients. The statistic for interobserver agreement in the selection of high-quality data sets was 0.88.

Classification according to HR Groups

Patients were classified in low HR (≤65 beats per minute), intermediate HR (66–79 beats per minute), and high HR (≥80 beats per minute) groups on the basis of two cutoff values (Fig 1).

ECG Pulsing Window

Patient characteristics are listed in Table 2.

The timing of the image reconstruction windows during ED and ES varied within the R-R interval (Table 3). In the low-HR group, reconstructed data sets in ED provided high quality in 93%

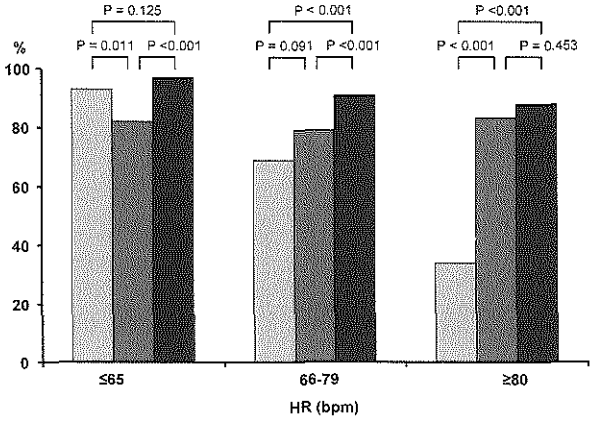


Figure 2. Frequency of High Quality Datasets in Three HR groups in End-diastole (ED) (light gray box) or End-systole (ES) (dark gray box) or both ED/ES (black box) on a per Patient level.

(118 of 127), without significant improvement (P = 0.13) by adding reconstructed data sets in ES. In the intermediate-HR group, reconstructed data sets in ES provided high quality in 79% (86 of 109), and reconstructed data sets in ED provided high quality in 69% (75 of 109). The availability of reconstructed data sets in both ES and ED significantly improved (P < 0.001) the number of high-quality data sets (91%, 99 of 109).

Table 3. Image Reconstruction Windows in Three HR Groups.

Heart rate (beats/minute)	End-Systole % R-R-interval	End-Diastole % R-R-interval
≤65	25-39%	60-76%
66-79	30-44%	61-77%
≥80	31-47%	65-75%

Values are the ranges of percentages of the R-R interval.

Table 2. Patient Demographics.

Characteristics	Overall	Group 1	Group 2	Group 3	Group 1 vs 2 P value	Group 1 vs 3 P value	Group 2 vs 3 P value
No. of patients	301	127	109	65	<0.001	<0.001	<0.001
Age (y)	63.6 ± 10.6	64.1 ± 9.4	63.0 ± 9.8	66.3 ± 11.4	0.537	0.056	0.018
Sex*							
M	215 (71%)	92 (72%)	77 (71%)	46 (71%)	0.760	0.807	0.986
F	86 (29%)	35 (28%)	32 (29%)	19 (29%)			
Body Mass Index (kg/m^2)	26.1 ± 3.4	26.4 ± 3.2	25.8 ± 4.0	25.7 ± 2.9	0.488	0.411	0.169
Average HR (beats/minute)	70.1 ± 13.3	55.4 ± 4.2	64.8 ± 2.5	90.3 ± 7.3	<0.001	<0.001	<0.001
Scan length, (cm)	12.0 ± 1.9	12.4 ± 2.1	12.0 ± 1.5	12.0 ± 1.1	0.022	<0.001	<0.05
Scan time (sec)	8.4 ± 1.9	9.8 ± 1.4	8.1 ± 0.8	6.6 ± 0.8	<0.001	<0.001	<0.001
Pitch	0.30	0.24	0.27	0.39	<0.001	<0.001	<0.001
Contrast load (mL)	74.0 ± 11.3	81.7 ± 7.6	72.9 ± 4.2	63.8 ± 4.4	<0.001	<0.001	<0.001
$CTDI_{vol}$ (mGy)	65.3 ± 17.2	75.7± 14.5	67.9 ± 16.1	53.5 ± 17.9	<0.001	<0.001	<0.001

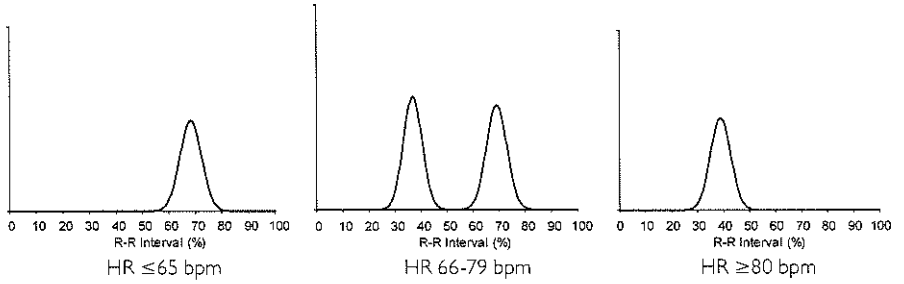
Group 1 had an HR of 65 beats per minute or less; group 2, an HR of 66–79 beats per minute; group 3, an HR of 80 beats per minute or more. Values are the mean ± standard deviation except where otherwise indicated. Numbers in parentheses are percentages. * P values are for comparison of men versus women.

In the high-HR group, reconstructed data sets in ES provided high quality in 83% (54 of 65), without significant improvement (P = 0.45) by adding reconstructed data sets in ED (Fig 2). On the basis of these observations, the optimal timing and width of the ECG pulsing window were determined for each HR group: 60%–76% of the R-R interval for low HRs, 30%–77% of the R-R interval for intermediate HRs, and 31%–47% of the R-R interval for high HRs (Fig 3).

Effective Dose

Instead of a fixed ECG pulsing window (25%–70% of the R-R interval), an optimized HR-dependent ECG pulsing protocol with a tube current outside the ECG pulsing window of 20% can help in reducing the effective dose of the CT examination by 41% (from 18.7 to 11.0 mSv) for patients with low HRs and by 37% (from 11.3 to 7.1 mSv) for patients with high HR (Table 4). The use of a reduced tube current outside the ECG pulsing window of 4% instead of 20% would have resulted in a further dose reduction of 38% (from 11.0 to 6.8 mSv) in patients with low HR and in a reduction of 41% (from 7.1 to 4.2 mSv) in patients with high HRs.

Figure 3. Width and Timing of ECG Pulsing Windows in the R-R-interval in Low (≤65 bpm), Intermediate (66-79 bpm) and High (≥80 bpm) Heart rates



In patients with intermediate HR, the width of the ECG pulsing window could not be narrowed without affecting image quality. However, the effective dose could be reduced by 9% (from 14.7 to 13.4 mSv) with a reduced tube current outside the ECG pulsing window of 4%.

Table 4. Effective Dose in DS Coronary CT Angiography.

ECG Pulsing Window and Tube Current	EED for All HRs (mSv)	EDD for HR ≤65 beats/min (mSv)	EDD for HR 66-79 beats/min (mSv)	EDD for HR ≥80 beats/min (mSv)
No pulsing	27.7	33.4	26.3	20.2
Wide pulsing*				
20% tube current	15.7	18.7†	14.7†	11.3†
4% tube current	13.2	15.8	12.4	9.5
Optimal pulsing‡				
20% tube current	11.8	11.0	15.6	7.1
4% tube current	8.6	6.8	13.4	4.2

Tube current is outside pulsing window. EED = estimated effective dose. * Wide pulsing window was 25%–70% of the R-R interval. †EED was based on Monte Carlo estimations by using volume CT dose index in each patient. ‡Optimal ECG pulsing windows were as follows: 60%–76% (HR, <65 beats/min), 30%–77% (HR, 66–79 beats/min), and 31%–47% (HR, <80 beats/min) of the R-R interval.

DISCUSSION

With the growth of cardiac CT use worldwide, concern has been raised about the rather high radiation exposure associated with coronary CT angiography (18,19). Optimization of scan protocols is therefore mandatory to keep the radiation exposure as low as reasonably achievable. It is important that referring physicians and operators are familiar with dose-saving algorithms that can be applied in coronary CT angiography. The tube current and tube voltage can be optimized according to the patient's habitus. Electrocardiographically controlled x-ray tube modulation, or ECG pulsing, represents another effective tool for use in the reduction of radiation exposure (20,21).

Hausleiter et al (22) demonstrated that the combination of a 100-kV scan protocol with ECG pulsing reduced the patient dose by 53% and 64% in 16- and 64-section coronary CT angiography, respectively.

In our study, we used a DS CT scanner equipped with ECG pulsing. The DS CT scanner allows high-quality scanning in patients with higher HR owing to improved temporal resolution (10–13). Because data were lacking about the potential effects of the width and timing of the ECG pulsing window on image quality and radiation exposure, we chose to use a relatively wide ECG pulsing window of 25%–70% of the cardiac cycle. This allowed us to study the optimal timing and width of the ECG pulsing window in patients with different HRs without compromising image quality.

Our results show that, in patients with a low HR (65 beats per minute), high-quality motion-free ED data sets were obtained in most (93%, n = 116) of the patients. This factor allowed us to safely use a narrow ECG pulsing window (60%–76% of the R-R interval) that did not affect image quality. In patients with an intermediate HR (between 66 and 79 beats per minute), the use of both ES and ED data sets allowed us to obtain high-quality data sets in most (91%, n = 99) patients. Therefore, narrow ECG pulsing during either ES or ED is not optimal. In this case, the use of a wide ECG pulsing window (30%–77% of the R-R interval), encompassing both the ES and ED is required to obtain high-quality images.

In patients with high HR (80 beats per minute), the ES data sets provided high-quality motion-free data sets in 83% (n = 56) of patients. Additional ED data sets did not improve the number of patients with high-quality data sets. This can be explained by the relatively short diastolic phase during higher HRs and, therefore, the absence of a motion-free period during the early and late diastolic filling phase and subsequent immediate atrial kick, all of which cause continuous displacement of the coronary arteries. Thus, ECG pulsing can be optimized in patients with high HRs by narrowing the ECG pulsing window width (31%–47% of the R-R interval). This finding is in agreement with the results of a study by Husmann et al (23) who investigated coronary artery motion during the cardiac phase in relation to HR and found that, with increasing HR, data sets with best image quality are reconstructed during earlier phases of the R-R interval.

The reduction in radiation exposure was considerable if one could use a narrow ECG pulsing window according to the HR. In patients with low HR (≤65 beats per minute), the radiation exposure was reduced to an effective dose of 11.0 mSv with reduced tube current outside the pulsing window of 20% of the nominal value to an effective dose of 6.8 mSv in the case of reduced tube current outside the pulsing window of 4% of the nominal value. It is of note that, in patients with low HR, the use of a narrow pulsing window is very effective in the reduction of patient dose because of the relatively long low-dose period of the long R-R interval.

In patients with intermediate HR (66–79 beats per minute), reduction in radiation exposure can be achieved only by using a reduced tube current at 4% of the maximum value in combination with a wide ECG pulsing window. However, the radiation exposure can be further reduced in patients with intermediate HR. Our data showed that, to acquire the data, there are potentially two narrow pulsing windows, 30%–44% and 61%–77% of the R-R interval, which would allow CT scanners the possibility of double pulsing (two peaks of nominal tube current during a single heartbeat) to use this scan protocol. For double pulsing, scanner technology should allow fast tube current transitions from nominal to low tube current and vice versa. To date, double pulsing is not yet clinically applicable in coronary CT angiography.

In patients with high HR (≥80 beats per minute), optimized ECG pulsing can help to decrease the effective dose to 7.1 mSv at 20% tube current outside the pulsing window or 4.2 mSv at 4% tube current outside the pulsing window. In this case, the reduction in radiation exposure is mainly the result of the high pitch and, hence, short scan time to cover the heart (14).

Our study had limitations. For the image quality evaluation, we took into account only the presence of coronary motion artifacts. Other image-degrading artifacts, such as low signal-to-noise ratio or calcium-related blooming artifacts, were not evaluated.

Our results show that the use of optimal ECG pulsing windows in relation to HR would result in a significant decrease in radiation exposure in coronary DS CT angiography. However, our findings were based on calculations and, therefore, only assumptions. Nevertheless, these assumptions appear reasonable and are taken from the technical properties of the DS CT scanner, properties that allow selection of narrow ECG pulsing windows in any phase of the cardiac cycle. However, prospective selection of these narrow pulsing windows for low and high HRs requires testing in the real clinical situation to demonstrate that these settings indeed do not compromise image quality.

In addition, prospective studies should provide evidence that the sensitivity and specificity to detect or rule out significant coronary artery disease are not negatively affected by the use of narrow ECG pulsing windows.

We did not evaluate the effect of other dose-saving algorithms, such as lower tube voltage or tube current, on image quality. It is expected that use of lower tube current–time product or tube voltage values in slim patients will further help to reduce patient dose estimates.

Our results apply only to DS CT scanners and may be different for other systems. In particular, the temporal resolution of 83 msec of the DS CT scanner, as compared with other scanners, allows the use of relatively smaller pulsing windows for high HRs.

In conclusion, the optimal phase of image reconstruction within the cardiac cycle strongly depends on the HR of the patient. Our results suggest that, with an optimized ECG pulsing strategy, radiation exposure can be greatly reduced while preserving image quality, particularly in patients with low or high HR.

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CHAPTER 10

PRESERVED DIAGNOSTIC PERFORMANCE OF DUAL-SOURCE CT CORONARY ANGIOGRAPHY WITH REDUCED RADIATION EXPOSURE AND CANCER RISK

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ABSTRACT

PURPOSE: To evaluate the effects of standard and optimal electrocardiographic (ECG) pulsing on diagnostic performance, radiation dose, and cancer risk in symptomatic patients in a "real-world" clinical setting.

MATERIALS AND METHODS: The institutional review board approved the study, and all patients gave informed consent. Dual-source computed tomographic (CT) coronary angiography was performed in 436 symptomatic patients (301 men, 135 women; mean age, 61.6 years ± 10.6 [standard deviation]; age range, 23-89 years) referred for conventional coronary angiography. Standard and optimal ECG pulsing was performed in 327 and 109 patients, respectively. The diagnostic performance of dual-source CT coronary angiography for detection of significant stenosis (≥50 luminal diameter reduction), with quantitative coronary angiography as the reference standard, was reported as sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios. The mean effective radiation dose, additional fatal cancer risk, and age- and sex-specific cancer risks related to one CT coronary angiographic examination were determined from data averaged over the study population.

RESULTS: Mean effective doses with standard and optimal ECG pulsing were 14.2 mSv ± 3.2 and 10.7 mSv ± 3.6, respectively. Optimal ECG pulsing resulted in a 43% overall reduction in mean effective radiation dose and cancer risk compared with a nonpulsing protocol (18.8 mSv ± 3.5) and a 25% overall reduction in mean effective dose compared with the standard pulsing protocol. At patient-by-patient analysis, CT coronary angiography with standard ECG pulsing yielded sensitivity, specificity, and positive and negative predictive values of 100% (95% confidence interval [CI]: 99%, 100%), 85% (95% CI: 81%, 88%), 94% (95% CI: 91%, 96%), and 99% (95% CI: 98%, 100%), respectively, for detection of significant stenosis. Optimal ECG pulsing yielded similar results: Sensitivity, specificity, and positive and negative predictive values were 100% (95% CI: 100%, 100%), 88% (95% CI: 82%, 94%), 97% (95% CI: 93%, 100%), and 100%, respectively.

CONCLUSIONS: Compared with a nonpulsing protocol, optimal ECG pulsing resulted in significant ($P < 0.001$) reductions in patient radiation dose and cancer risk (up to 55% reduction in patients with high heart rates) while preserving the diagnostic performance of dual-source CT coronary angiography.

INTRODUCTION

Computed tomographic (CT) coronary angiography has emerged as an attractive noninvasive diagnostic modality for detecting or ruling out significant coronary artery disease. The number of patients who undergo CT coronary angiography is steadily growing, and there is increasing scrutiny of the radiation dose delivered during this examination (1). Einstein et al (2) recently demonstrated that radiation exposure from 64-section CT coronary angiography is associated with a relatively wide variation in lifetime attributable risk of cancer in relation to patient age and sex. Consideration of radiation issues is particularly warranted in young women, who are the most vulnerable to radiation exposure (2).

State-of-the-art 64-section CT scanners now enable one to accurately detect or rule out significant coronary artery stenosis in symptomatic patients. The dual-source 64-section CT scanner is characterized by two acquisition systems—an x-ray tube system and the corresponding detector system—with an angular offset of 90°. This scanner design results in a heart rate–independent temporal resolution of 83 msec (3). Results of relatively recent studies indicate that dual-source CT coronary angiography has high diagnostic accuracy, with sensitivity ranging from 93% to 100% and specificity ranging from 82% to 90%, without use of additional prescanning β-blockers (4–7).

The dual-source CT scanner is equipped with dose-saving algorithms such as adaptive electrocardiographic (ECG) pulsing, which, when properly used, can substantially reduce the patient radiation dose while preserving diagnostic image quality (8). Before performing CT, the operator can select a time window, or ECG pulsing window, within the cardiac cycle during which the patient will be fully exposed to radiation (at nominal tube current) and imaging data will be acquired, while outside of this pulsing window the tube current will be reduced to 20% (standard protocol) or 4% (optimal protocol) of the nominal value.

The purpose of this study was to evaluate the effects of standard and optimal ECG pulsing on patient dose and diagnostic performance in a symptomatic patient population. We also sought to obtain quantitative estimates of cancer risk for this population according to the internationally accepted International Commission on Radiological Protection (ICRP) recommendations (9) and the Biological Effects of Ionizing Radiation (BEIR) VII approach (10).

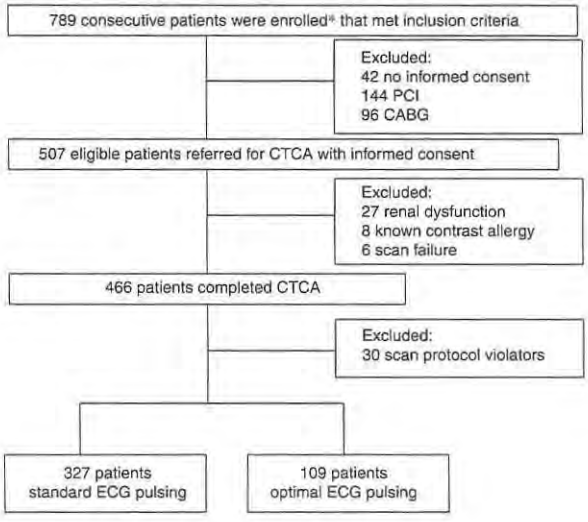
MATERIALS AND METHODS

Study Population

Between April 2006 and September 2008, 789 patients referred for invasive diagnostic coronary angiography were screened for CT coronary angiography (Fig 1). Only those patients with a sinus rhythm were included. Exclusion criteria were substantial renal dysfunction (serum creatinine level > 120 mmol/mL, n = 27), known allergy to contrast material (n = 8), previous percutaneous (n = 144) or surgical (n = 96) revascularization, and violation of scanning proto-

Figure 1. Flow diagram.

Flowchart of patient exclusion and inclusion for CT coronary angiography (CTCA) with ECG pulsing. Period of enrollment (*) was April 2006 to September 2008. CABG = coronary artery bypass graft, PCI = percutaneous coronary intervention.



cols (n = 30). An additional 48 patients were excluded because they did not provide informed consent or CT scanning was not successfully completed. Thus, our final study population comprised 436 patients (overall mean age, 61.6 years ± 10.6 [standard deviation]; age range, 23–89 years): 301 men (mean age, 60.4 years ± 10.8; age range, 23–89 years) and 135 women (mean age, 59.7 years ± 11.2; age range, 27–86 years). The institutional review board approved the study, and all included patients gave informed consent.

CT Scanning Protocol

Patients were scanned with use of a dual-source CT scanner (Somatom Definition; Siemens Medical Solutions, Forchheim, Germany). No β-blockers were administered before scanning. Patients received 0.4 mg of nitroglycerin sublingually just before scanning.

CT coronary angiography scanning parameters were as follows: two x-ray tubes, detector collimation of 32 x 0.6 mm per tube with double sampling by means of rapid alteration of the focal spot in the longitudinal direction (z-flying focal spot) (11), rotation time of 330 msec, tube voltage of 120 kV, and full tube current of 625 mA per tube (independent of patient size). The pitch varied between 0.20 for slow heart rates (40 beats per minute) and 0.53 for fast heart rates (100 beats per minute), with pitches individually adapted for heart rates faster than 40 beats per minute and slower than 100 beats per minute.

A 60–100-mL (dependent on expected scanning time) bolus of iodinated contrast material (iopromide, 370 mg of iodine per milliliter, Ultravist; Schering, Berlin, Germany) was injected into an antecubital vein at a flow rate of 5.5 mL/sec and followed by a 40-mL saline chaser, which was also injected at a flow rate of 5.5 mL/sec. A bolus-tracking technique was applied to synchronize the data acquisition with the arrival of contrast material in the coronary arteries.

All patients were scanned with ECG pulsing (Fig 2). The first 327 patients enrolled were scanned from April 2006 to November 2007, with standard ECG pulsing applied by using a fixed pulsing

window; the full tube current was applied at 25%–70% of the R-R interval. Outside the ECG pulsing window, the tube current was reduced to 20% of the full current. The 109 patients subsequently enrolled were scanned from November 2007 to September 2008, with optimal ECG pulsing applied by using validated ECG pulsing windows during end-diastole (60%–76% of R-R interval) for low heart rates (≤65 beats per minute), during end-systole (31%–47% of R-R interval) for high heart rates (≥80 beats per minute), and during both end-diastole and

Figure 2A. Schematic view of ECG pulsing.

Schematic view of ECG pulsing. Top row: Full radiation exposure during entire R-R interval (no ECG pulsing). Middle row: ECG pulsing with full radiation exposure during middle- to end-diastole; exposure is reduced to 20% of maximum outside ECG pulsing window. Bottom row: ECG pulsing with full radiation exposure during middle- to end-diastole; exposure is reduced to 4% of maximum outside ECG pulsing window.

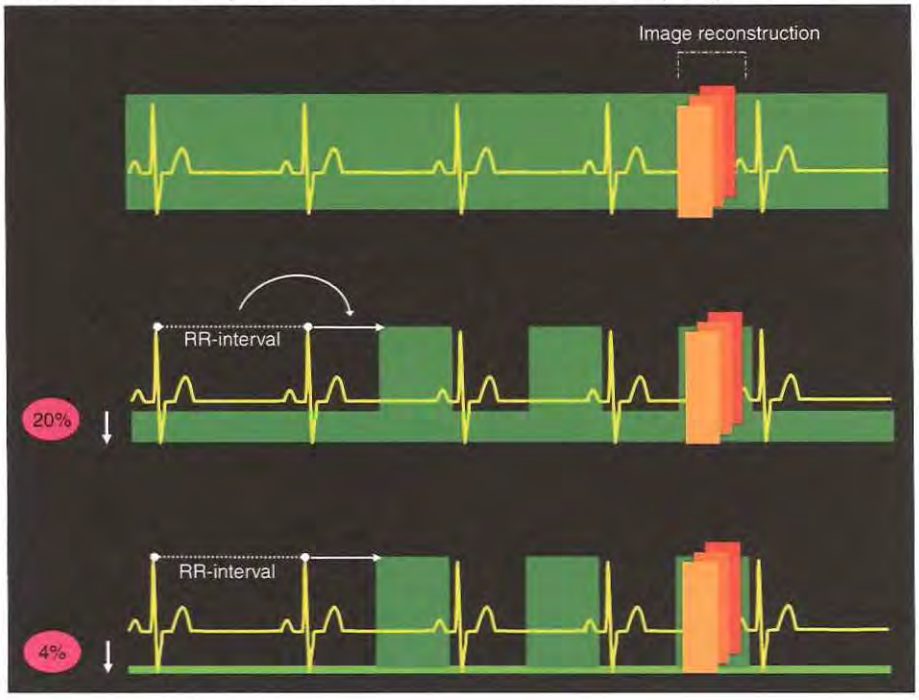
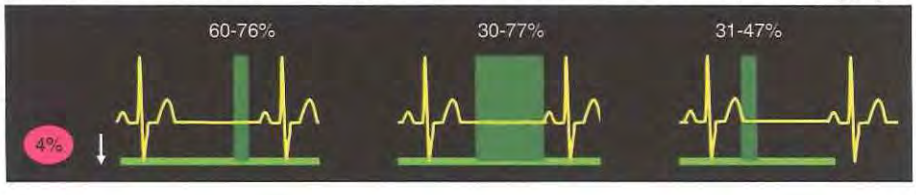


Figure 2B. Schematic view of optimal ECG pulsing.

Schematic view of optimal ECG pulsing at 60%–76% of R-R interval in patients with heart rates of 65 or fewer beats per minute (left), 30%–77% of R-R interval in patients with heart rates of 66–79 beats per minute (middle), and 31%–47% of R-R interval in patients with heart rates of 80 or more beats per minute (right).



end-systole (30%–77% of R-R interval) for intermediate heart rates (66–79 beats per minute) (12). Outside the ECG pulsing window, the tube current was reduced to 4% of the full current with use of a dose-reduction tool (Mindose; Siemens Medical Solutions). All CT data sets were reconstructed by using a single-segment reconstruction algorithm, which resulted in a temporal resolution of 83 msec, a section thickness of 0.75 mm in 0.4-mm increments, and medium-to-smooth (B26f) and sharp (B46f) convolution kernels. The resultant ranges of in- and through-plane spatial resolution were 0.6–0.7 mm and 0.4–0.5 mm, respectively (3).

Diagnostic Performance

One experienced cardiologist (E.N., 5 or more years experience), who was unaware of the CT coronary angiography results, identified all available coronary segments at conventional invasive coronary angiography by using a 17-segment modified American Heart Association classification system (13). All segments, regardless of their size, were included for comparison with the segments depicted at CT coronary angiography. The segments were visually classified as being normal, having luminal irregularity (<20% reduction in luminal diameter), or having disease (>20% reduction in luminal diameter). The diseased segments were evaluated by using a validated quantitative coronary artery algorithm (CAAS; Pie Medical, Maastricht, the Netherlands). Segments with a 50% or greater reduction in luminal diameter in two orthogonal planes were considered to have significant stenosis. Two experienced observers (A.C.W., N.R.M., 4 or more years of CT coronary angiography training), who were unaware of the invasive coronary angiography results, scored all CT data sets and identified the significant stenoses. Interobserver disagreements were resolved by consensus in a joint session.

Patient Radiation Dose

The effective radiation dose and organ equivalent doses delivered to the patient during one CT coronary angiographic examination with the standard and optimal ECG pulsing protocols were estimated for each patient by using Monte Carlo simulations (ImPACT, version 0.99w; St George's Hospital, Tooting, London, England). This software includes no data that can be applied to the dual-source CT scanner that we used. Therefore, we performed calculations for a 64-section single-source CT scanner (Sensation; Siemens Medical Solutions) and adapted them to our 64-section dual-source CT scanner by using the volume CT dose index (CTDIv) values from the scanner console. Standard and optimal ECG pulsing protocols were compared with a nonpulsing protocol. For each patient, the CTDIv with no pulsing (CTDIv-np) was calculated by using the following formula: CTDIv-np = CTDIw-np/p-CTDIw-np = 23.3 mGy, where CTDIw-np is the weighted CT dose index with no pulsing and p-CTDIw-np is the pitch with CTDIw-np.

Cancer Risk Estimates

From the effective dose, estimates of the risk of additional fatal cancer (based on ICRP approach) from a single CT coronary angiographic examination were made by using a risk factor of 0.05 per sievert (9). This risk factor does not apply to individuals. Therefore, the patient sex–dependent and patient age–dependent whole-body lifetime attributable risk of cancer incidence and mortality (based on BEIR VII approach) from a single CT coronary angiographic

examination was estimated by using patient age, patient sex, and organ-specific lifetime attributable risks (10). Risks were estimated for 50-, 60-, and 70-year-old men and women, who were representative of the patients examined in this study.

Statistical Analyses

Continuous variables were expressed as means ± standard deviations, and categorical characteristics were expressed as numbers and percentages. Differences in continuous and categorical variables between the patients scanned with standard ECG pulsing and those scanned with optimal ECG pulsing were calculated by using the Student t test and the Mann-Whitney U test, respectively. The diagnostic performance of CT coronary angiography in the detection of significant coronary artery stenosis, with the quantitative coronary artery algorithm as the reference standard, was reported in terms of sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios (with corresponding 95% confidence intervals). CT coronary angiography was compared with the quantitative coronary artery algorithm on a patient-by-patient basis (no stenosis or any significant stenosis per patient). Inter- and intraobserver variability in the detection of significant coronary artery stenosis was calculated by using statistics. To determine intraobserver variability, one observer (A.C.W., 4 or more years experience in CT coronary angiography) evaluated 130 (30%) of the 436 CT data sets twice, with an interval of 4 weeks between the two evaluations.

The data were clustered, implying that potential correlations existed between the multiple (n = 17) segments analyzed in each patient. To adjust for the clustered nature of the data, we used a bootstrap approach for the analyses. We obtained a total of 1000 replications by sampling segments (with replacement), with the patient as cluster (14,15). Results were reported in accordance with STARD (Standards for Reporting of Diagnostic Accuracy) criteria (16). The statistical analyses were performed by using SPSS, version 12.1 (SPSS, Chicago, Ill), and Stata, version SE 8.2 (Stata, College Station, Tex), software.

RESULTS

Patient and CT scanning characteristics are listed in Table 1. We found no significant difference in age between the male and female patients ($P = 0.26$).

Diagnostic Performance

The diagnostic performance of CT coronary angiography in the detection of significant coronary artery stenosis at patient-by-patient analysis is detailed in Table 2. Values for inter- and intraobserver variability in the detection of significant stenosis on a per-patient basis were 0.90 and 0.95, respectively, with consensus reading performed owing to disagreements regarding eight patients. Agreement analysis to investigate the effect of the clustered nature of the data revealed practically identical results, which indicated a negligible correlation between observations within each patient. Per-segment analysis findings were confirmed with bootstrap analysis. We ob-

Table 1. Patient and CT Scanning Characteristics.

No. of patients	327	109	p-value
No. of male patients	226 (69)	75 (69)	0.91
Age (y)*	61.5±10.7	61.9±10.4	0.78
Clinical Presentation			
Typical angina	147 (45)	61 (56)	0.03
Atypical angina	160 (49)	44 (40)	0.17
Unstable chest pain	35 (11)	6 (4)	0.11
Risk factors			
Hypertension	129 (40)	52 (48)	0.08
Hypercholesterolemia	182 (56)	61 (56)	0.82
Smoker	100 (31)	23 (21)	<0.001
Diabetes Mellitus	70 (21)	13 (12)	0.05
Family history of CAD	170 (52)	53 (49)	0.67
CT Coronary Angiography			
Scan length (cm)	11.1 ± 2.8	11.0 ± 2.9	0.87
Scan time (sec)	8.8 ± 1.9	8.6 ± 1.7 sec	0.51
Heart rate (beats/min)	69.8 ± 23.9	68.8 ± 22.7	0.86
$CTDI_v$	64.1 ± 14.3	48.5 ± 13.7	<0.001

Data for 436 patients are presented. Numbers in parentheses are percentages. CAD = coronary artery disease, CTDIv = volume CT dose index. * Means ± standard deviations.

served no significant difference in diagnostic performance between CT coronary angiography performed with standard ECG pulsing and that performed with optimal ECG pulsing.

Effective Dose and Cancer Risk Estimates

Standard ECG pulsing in the first 327 patients enrolled resulted in a 22% overall reduction in mean effective radiation dose (14.2 mSv ± 3.2) compared with a nonpulsing protocol (18.1 mSv ± 4.0). Optimal ECG pulsing in the 109 subsequently enrolled patients resulted in a 43% overall reduction in mean effective dose (10.7 mSv ± 3.6) compared with a nonpulsing protocol (18.8 mSv ± 3.5). Optimal ECG pulsing resulted in a 25% overall reduction in mean effective dose (10.7 mSv ± 3.6) compared with the standard pulsing protocol (14.2 mSv ± 3.2). The effective dose and additional fatal cancer risk estimates (based on ICRP approach) with optimal ECG pulsing in patients with low (≤65 beats per minute), intermediate (66–79 beats per minute), and high (≥80 beats per minute) heart rates are shown in Table 3 and Figure 3. Use of optimal ECG pulsing compared with use of a nonpulsing protocol resulted in significant ($P < 0.001$) reductions in mean effective radiation dose of 53%, 23%, and 55% in patients with heart rates of 65 or fewer beats per minute, 66–79 beats per minute, and 80 or more beats per minute, respectively, as well as significant reductions in additional cancer risk estimates (based

Table 2. Diagnostic Performance of Dual-Source CT Coronary Angiography in Detection of Significant Stenosis.

ECG pulsing	Disease Prevalence (%)	No. of Patients	TP Findings	TN Findings	FP Findings	FN Findings	Sensitivity* (%)	Specificity* (%)	PPV* (%)	NPV* (%)	PLR	NLR
Standard	70	327	229	82	15	1	100 (99, 100)	85 (81, 88)	94 (91, 96)	99 (98, 100)	6.44	0.01
Optimal	76	109	83	23	3	0	100 (100, 100)	88 (82, 94)	97 (93,100)	100	8.67	0.00

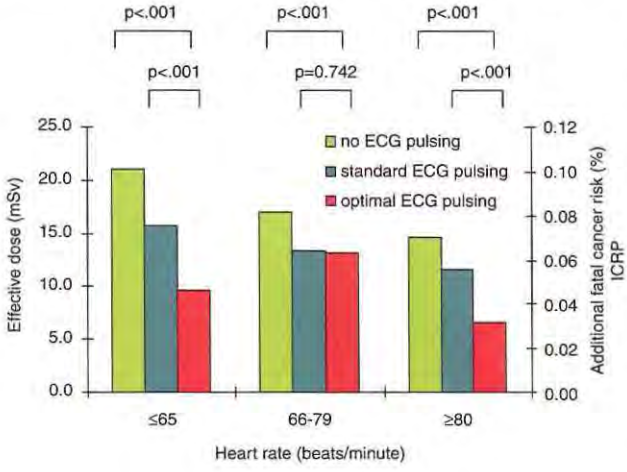
FN = false-negative, FP = false-positive, NLR = negative likelihood ratio, NPV = negative predictive value, PLR = positive likelihood ratio, PPV = positive predictive value, TN = true-negative, TP = true-positive. * Numbers in parentheses are 95% confidence intervals.

Table 3. Reductions in Effective Radiation Dose with Optimal ECG Pulsing.

	Effective Radiation Dose (mSv)*			Dose Reduction with Optimal ECG Pulsing (%)	
Heart rate (beats/minute)	No ECG pulsing	Standard ECG pulsing	Optimal ECG pulsing	Compared with Standard ECG pulsing	Compared with No ECG pulsing
≤ 65	20.5 ± 3.2	15.8 ± 2.9	9.6 ± 2.3	39.2	53.2
66-79	17.1 ± 2.3	13.4 ± 2.5	13.2 ± 2.1	1.5	22.8
≥ 80	14.7 ± 3.9	11.7 ± 3.3	6.6 ± 1.2	43.6	55.1

* Mean effective radiation doses ± standard deviations.

Figure 3. Graph illustrates effective doses and additional fatal cancer risks (based on ICRP recommendations) associated with standard and optimal ECG pulsing versus no ECG pulsing.



on ICRP approach) ($P < 0.001$). Use of optimal ECG pulsing compared with use of a standard pulsing protocol resulted in significant ($P < 0.001$) radiation dose reductions of 39% and 44% for patients with heart rates of 65 or fewer beats per minute and 80 or more beats per minute, respectively, as well as significant ($P < 0.001$) cancer risk reductions. In patients with heart rates of 66–79 beats per minute,

Figure 4A. Whole-body lifetime attributable risk (LAR) of cancer incidence (Biological Effects of Ionizing Radiation -BEIR- VII approach).

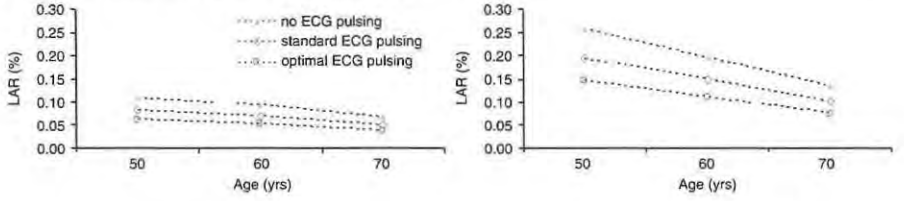
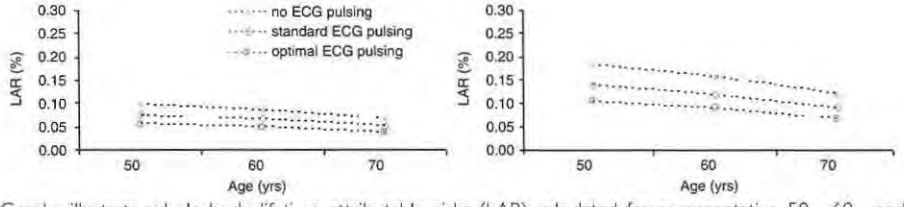


Figure 4B. Whole-body lifetime attributable risk (LAR) of mortality (Biological Effects of Ionizing Radiation -BEIR- VII approach).



Graphs illustrate whole-body lifetime attributable risks (LAR) calculated for representative 50-, 60-, and 70-year-old male and female patients on the basis of the mean age for the study population (61.6 years ± 10.6). (a) Cancer incidence and (b) fatal cancer incidence data for male (left) and female (right) patients are shown. The lifetime attributable risks between these ages were interpolated (dotted lines).

reductions in mean effective dose (1.5%) and additional cancer risk estimates were not significant ($P > 0.05$).

The mean age for our study population was 61.6 years ± 10.6. The effects of standard and optimal ECG pulsing, as compared with a nonpulsing protocol, on whole-body lifetime attributable risk of cancer incidence and mortality (based on BEIR VII approach) in 50-, 60-, and 70-year-old male and female patients are shown in Figure 4.

DISCUSSION

The rapid increase in multidetector CT examinations performed in patients with heart conditions has raised concern about the increasing radiation exposure to patients. Although we are concerned because CT coronary angiography is associated with an additional risk of cancer, our perception of risk is not quantified (17). The cancer risk estimates reported in our study were derived from the ICRP recommendations and the BEIR VII approach. These models may be subject to criticism, but they are internationally recognized approaches to estimating risk of cancer induced from radiation exposure (2). Application of the BEIR VII model indicates that in our population, the cancer risk was relatively low for male patients compared with the general ICRP estimate. For female patients, the risk approximately doubles because of the direct irradiation of the sensitive female breast tissue in CT coronary angiography. However, our study population was relatively old (mean age, 61.6 years): It comprised only three female patients younger than 35 years. These factors indicate that CT coronary angiography is not regularly performed in young women.

In a previous study, the optimal ECG pulsing windows and expected dose reduction were theoretically calculated on the basis of image quality assessment (12). In the current study, we prospectively validated the effects of optimal ECG pulsing windows on diagnostic performance, radiation dose, and cancer risk. The dose reduction achieved (up to 55%) was somewhat lower than the expected dose reduction based on theoretic calculations (up to 65%) because the adaptive ECG pulsing sequence reacts to sudden changes in the R-R interval (eg, occurrence of a premature beat) with a change in tube current modulation during the successive heart beats. This allows the operator to reconstruct additional data sets and improve image quality and diagnostic performance at the cost of a higher radiation dose. With use of the linear no-threshold model of the BEIR IV approach, the percentage cancer risk reduction equals the percentage dose reduction achieved. The absolute risk itself depends on the patient's age and sex. Because relatively young female patients have the highest risk, the effect of dose reduction is expected to be relatively large in this subgroup.

In our study, we achieved favorable results in a real-world symptomatic patient population while preserving diagnostic performance. To put our results in perspective, it is important to note that the additional radiation-induced cancer risk that we calculated was substantially lower than the reported 1:3 overall lifetime risk of cancer (18).

Clinical Implications

Referring physicians should be aware of the biologic effects of ionizing radiation and the associated cancer risk, and patients should be referred for CT coronary angiography in accordance with recommendations of the Euratom Directive (18) and the American College of Radiology white paper on radiation dose (19). The practitioner is ultimately responsible for the technical and clinical success, complications, and risks associated with the procedure and should be adequately informed about the clinical indication for CT coronary angiography based on type of chest pain, stress test results, and patient characteristics (age, sex, known risk factors for coronary artery disease). To justify the amount of individual radiation exposure rendered at CT coronary angiography, the diagnostic benefits should outweigh the radiation burden. The effectiveness, benefits, and risks of alternative techniques that involve no exposure or less exposure to ionizing radiation should be considered (20,21).

The mean effective dose (10.7 mSv) delivered at CT coronary angiography with optimal pulsing in this study was still higher than reported doses delivered at diagnostic invasive coronary angiography (3–10 mSv) (22). However, when CT coronary angiography is being considered as an alternative to invasive coronary angiography, it is important to assess the overall risk of mortality associated with each procedure. The overall risk associated with invasive coronary angiography is the sum of radiogenic and procedural risks, such as risks of mortality (rare), myocardial infarction, stroke, or bleeding, which reportedly yields an overall risk of 0.13% (23). Both angiographic techniques are associated with contrast agent allergic reactions and renal function deterioration. The overall risk associated with invasive coronary angiography, 0.13%, is higher than the reported overall risk of 0.07% associated with CT coronary angiography (23). This finding supports the notion that CT coronary angiography is an attractive alternative to invasive coronary angiography in selected patients with low to intermediate estimated pretest probability of significant coronary artery disease. In patients with a high estimated risk of coronary artery disease, CT coronary angiography does not yield additional diagnostic information, and, thus, direct referral for invasive coronary angiography is recommended (24).

Limitations

We used dose estimates based on parameters and settings for the 64-section single-source Sensation scanner because at the time of this writing, no software applicable to the dual-source Definition scanner settings was commercially available. The volume CT dose indexes for a nonpulsing protocol were theoretically calculated because our adherence to the ALARA (as low as reasonably achievable) principle did not allow us to perform CT coronary angiography without ECG pulsing. The mean effective doses were calculated from doses averaged over the study population, and because the protocols were modified on the basis of heart rate and the fatal cancer risk calculations were age dependent, the values averaged for this population may not necessarily reflect all populations. Manual or automatic adjustment of the tube current or voltage to patient size or body mass index is warranted to further reduce radiation exposure (25), but it requires more clinical testing.

Our results reflect the estimated doses and diagnostic performance with a dual-source CT scanner and are therefore vendor, scanner, and protocol specific. In one study involving the use of a single-source 64-section CT scanner with a relatively slow table feed (pitch, 0.16–0.22), a mean effective dose of 20.0 mSv ± 3.5 was reportedly delivered with use of ECG pulsing (26). Hausleiter et al (27) reported an overall mean radiation dose of 9.4 mSv ± 1.0 that was delivered by using conventional single-source 64-section CT scanners with ECG pulsing. This dose is reasonably comparable to the mean dose of 10.7 mSv ± 3.6 delivered to the patients scanned with optimal ECG pulsing at dual-source CT coronary angiography in our study.

In our study, all patients were scanned with use of retrospective ECG gating and hence were exposed to some level of radiation during the CT angiographic examination. The use of retrospective ECG gating, however, enabled us to study the effect of optimal ECG pulsing on patients with various heart rates without administering a prescan β-blocker. Despite significant reductions in the mean effective dose to patients with low and high heart rates (9.6 mSv and 6.6 mSv, respectively), the doses to patients with intermediate heart rates remained relatively high (13.2 mSv). Thus, the use of prescan β-blockers to lower the heart rate to 65 or fewer beats per minute seems justified for patients with intermediate heart rates and the consequent overall dose of less than 10 mSv delivered to all patients. Alternatively, prospective ECG triggering or the step-and-shoot scanning mode (28–31) can be used in multisection CT coronary angiography: The table is stationary during data acquisition; then it moves to the new starting position for the next x-ray beam rotation. The generation of x-rays is stopped between two consecutive scan acquisitions. To date, this low-dose (1–5 mSv) sequential scanning technique can be applied safely in only those patients with low and regular heart rhythms. Compared with spiral CT, however, step-and-shoot CT is more susceptible to heart irregularities and sudden increases in heart rate and generally requires repeat scanning in these patients. Furthermore, the repeat scanning is performed at the expense of an overall higher dose and requires a second injection of iodinated contrast material.

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CHAPTER 11

IMPACT OF HEART RATE FREQUENCY AND VARIABILITY ON RADIATION EXPOSURE, IMAGE QUALITY, AND DIAGNOSTIC PERFORMANCE IN DUAL-SOURCE SPIRAL CT CORONARY ANGIOGRAPHY

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ABSTRACT

PURPOSE: To investigate the impact of heart rate frequency (HRF) and heart rate variability (HRV) on radiation exposure, image quality, and diagnostic performance to detect significant stenosis (≥50% lumen diameter reduction) using adaptive ECG pulsing at dual-source spiral CT coronary angiography (CTCA).

MATERIAL AND METHODS: Institutional review committee approval and informed consent was obtained in all patients. No pre-scan beta-blockers were applied prior to scanning. Non-contrast CT and CTCA using adaptive ECG pulsing was performed in 927 consecutive patients (600 men; 327 women, mean age 60.3±11.0 years). Patients were divided into 3 HRF groups: low (≤65 bpm), intermediate, (66-79 bpm), and high (≥80 bpm), and 4 HRV groups on the basis of the mean inter-beat difference (IBD) during CTCA acquisition: normal (0-1 IBD), minor (2-3 IBD), moderate (4-10 IBD) and severe (>10 IBD). Radiation exposure and image quality regarding the presence of motion artifacts were evaluated in all patients. Diagnostic performance was presented as sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios with corresponding 95% confidence intervals (CIs) in a subpopulation of 444 patients using quantitative coronary angiography as reference standard.

RESULTS: CT coronary angiography yielded good image quality in 98% of patients and no significant differences in image quality were found among HRF and HRV groups. Radiation exposure was significantly higher in patients with low versus high HRF and in patients with severe versus normal HRV. No significant differences among HRF and HRV groups in image quality and diagnostic performance were found. A nonsignificant trend was found toward a lower specificity and PPV in patients with a high HRF or severe HRV when compared with low HRF or normal HRV in patients with a low calcium score (Agatston score <100).

CONCLUSIONS: Dual-source spiral CT coronary angiography using adaptive ECG pulsing results in preserved diagnostic image quality and performance independent of heart rate frequency or heart rate variability at the cost of limited dose reduction in arrhythmic patients.

INTRODUCTION

Spiral CT coronary angiography (CTCA) has emerged as a non-invasive diagnostic modality that reliably excludes the presence of significant coronary artery disease (1, 2).

Dual-source CT scanners are equipped with 2 X-ray sources and provide a heart rate independent temporal resolution of 83 ms. Such improved temporal resolution may allow more reliable detection or exclusion of significant coronary artery stenosis in patients with fast or irregular heart rates. However, the radiation exposure associated with spiral CT is relatively high (3-5).

ECG-controlled X-ray tube current modulation or 'ECG-pulsing' has been introduced as an effective tool to reduce radiation exposure up to 50% in spiral CTCA (6, 7). The first generation ECG-pulsing algorithms were not standard used because the occurrence of a single premature beat could result in non-diagnostic image quality due to incorrect timing of the high X-ray tube output. Currently available ECG-pulsing algorithms are able to detect ectopic heart beats and the X-ray tube current modulation is automatically switched off until the heart rate is stable again. Such adaptive ECG-pulsing algorithms in spiral CT are designed to maintain diagnostic image quality in arrhythmic patients since the continuous high X-ray tube output allows flexible selection of the desired reconstruction phase throughout the R-R interval. However, image quality is only maintained at the cost of higher radiation exposure (8).

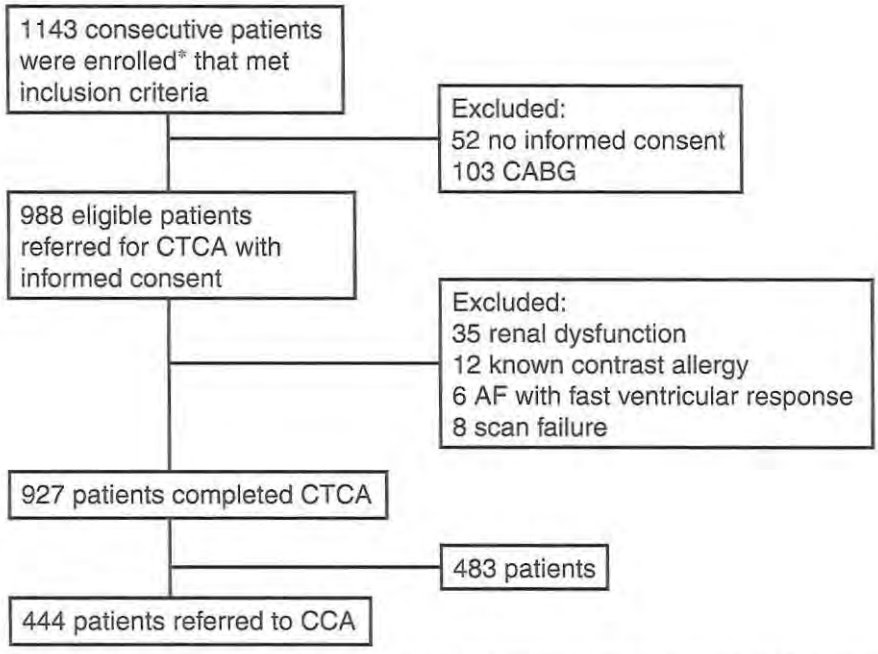
The purpose of this study was to determine the impact of heart rate frequency (HRF) and heart rate variability (HRV) on radiation exposure and image quality in a large cohort of patients undergoing Dual-source CTCA with adaptive ECG-pulsing. In addition, we evaluated the impact of HRF and HRV on the diagnostic performance of Dual-source CTCA to detect or rule out significant stenoses in a subgroup of patients who underwent additionally conventional coronary angiography (CCA).

MATERIAL AND METHODS

Study Population

During a period from April 2006 to October 2008, 1143 consecutive symptomatic patients with suspected or known coronary artery disease were eligible for inclusion in the study (Figure 1). Excluded were patients with previous surgical revascularization (n=103) and with atrial fibrillation with a fast ventricular response (n=6). CTCA-specific exclusion criteria were known allergy to Iodinated contrast material (n=12) and impaired renal function (serum creatinine >120 μmol/l) (n=35). Thus, the study population comprised 927 patients (600 men; 327 women, mean age 60.3±11.0 years). The institutional review board approved the study and all patients gave informed consent.

Figure 1. Flow Diagram.



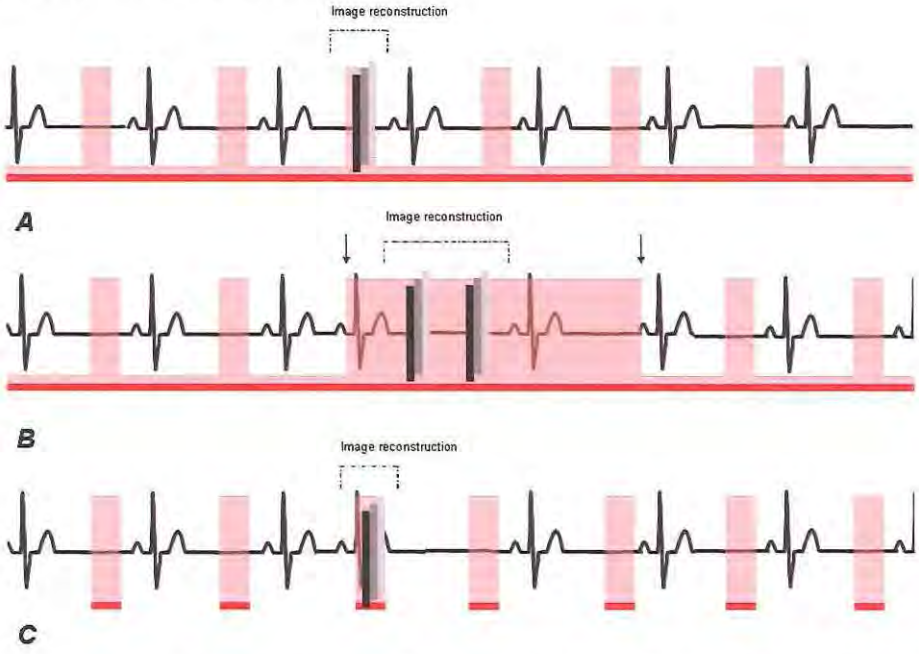
Flowchart of study patients. AF = atrial fibrillation, CABG = coronary artery bypass graft, CCA = conventional coronary angiography, CTCA = CT coronary angiography. * = Period of enrollment: April 2006 to October 2008.

Scan Protocol

Patients were scanned using a Dual-source CT scanner (Somatom Definition, Siemens Healthcare, Forchheim, Germany). No beta-blockers were administered prior to the scan. Patients received Nitroglycerin (0.4 mg) sublingually just before scanning. A non-enhanced calcium scoring scan was performed prior to CTCA. CTCA scan parameters were: number of X-ray tubes 2, detector collimation 32 x 0.6 mm per tube with double sampling by rapid alteration of the focal spot in the longitudinal direction (z flying focal spot) (9), rotation time 330 ms, tube voltage 120 kV, full tube current 625 mA per tube, independent of patient size. Prior to scanning, the pitch was set automatically by the scanner's software. Pitch varied between 0.20 for low HRF (<40 bpm) and 0.53 for high HRF (>100 bpm), with individually adapted pitch values for HRF >40 and <100 bpm.

A bolus of iodinated contrast material (Ultravist® 370 mgI/ml, Schering AG, Germany), which varied between 60-100 ml depending on the expected scan time, was injected (flow rate: 5.5 ml/s) in an antecubital vein followed by a saline chaser (40 ml; flow rate: 5.5 ml/s). A bolus tracking technique was applied to synchronize the data acquisition with the arrival of contrast in the coronary arteries.

Figure 2. Schematic illustrations of adaptive ECG pulsing in spiral dual-source CTCA (A, B) and Step-and-Shoot (SAS) scan mode (C).



A: Spiral CTCA in a low and regular heart rate. The ECG pulsing window is set during mid-to-end diastole and radiation exposure is reduced outside the ECG pulsing window. The red line correlated with X-ray tube output, the pink bar indicates full or reduced X-ray tube output.

B: Spiral CTCA in a low and irregular heart rate. The adaptive ECG pulsing algorithm adapts to the occurrence of a premature beat by switching off the ECG pulsing algorithm and full X-ray is given during two subsequent heart beats (between arrows). Image reconstruction is performed by manual repositioning of the reconstruction windows as previously described (12).

C: Step-and-shoot (SAS) CTCA in a low and irregular heart rate. Full X-ray during predefined time intervals in the cardiac cycle is given and image reconstruction can only be performed during the premature ectopic beat resulting in severe motion artifacts.

All patients were scanned using an adaptive ECG pulsing algorithm (Figure 2).

The first enrolled 640 patients were scanned from April 2006 to November 2007 and standard ECG pulsing was applied using a fixed pulsing window (full tube current was given from 25 to 70% of the R-R-interval). Outside the ECG pulsing window, the tube current was reduced to 20% of the full current. The subsequent 287 patients were scanned from December 2007 to September 2008 and optimal ECG pulsing was applied using validated ECG pulsing windows during mid-to-end-diastole (60-76% of R-R-interval) in low HRF (≤65 bpm), during end-systole (31-47%) for high HRF (≥80 bpm), and during both mid-to-end-diastole and end-systole (30-77%) for intermediate HRF (66-79 bpm), respectively (6). Outside the ECG

pulsing window the tube current was reduced to 4% of the full current (Mindose®, Siemens Healthcare, Forchheim, Germany).

CT Image Reconstruction

All CTCA datasets were reconstructed using a single-segment reconstruction algorithm resulting in 83 ms temporal resolution; slice thickness 0.75 mm; increment 0.4 mm; medium-to-smooth (B26f) and sharp (B46f) convolution kernel. Standard reconstruction algorithms were applied using an absolute reverse or percentage technique to obtain datasets during end-systole and/or mid-to-end diastole according to heart rate frequency (6). In case the standard reconstruction algorithm provided datasets with insufficient image quality of one or more coronary segments, additional datasets were manually reconstructed. If necessary, multiple datasets of a single patient were used separately in order to obtain optimal image quality for all coronary segments. Image reconstruction windows were manually repositioned to achieve high image quality in patients with arrhythmia, as previously described (12). For CTCA analysis, the best selected datasets were transferred to an offline work-station (MMWP®, Siemens Healthcare, Forchheim, Germany).

Quantitative Coronary Angiography (QCA)

A subpopulation of patients (48%, 444/927) underwent CCA. All conventional angiograms were carried out within four weeks before or after CCA. Three experienced cardiologists (R.N.E., S.K, and C.A.M., 5 or more years of interventional cardiology experience) unaware of the results of CTCA, identified all available coronary segments at invasive CA using a 17-segment modified American Heart Association (AHA) classification (10). All segments, irrespective of size, were included for comparison with CTCA. Segments were visually classified as normal or luminal irregularities (<20% lumen diameter reduction), or diseased (≥20% lumen diameter reduction). The stenoses in segments visually scored as having more than 20% narrowing, were quantified by a validated quantitative coronary angiography (QCA) algorithm (11). Stenoses were evaluated in the worst angiographic view and classified as significant if the lumen diameter reduction was 50% or more.

CT image evaluation

The total calcium scores (Agatston score) per patient were calculated using dedicated software (Syngo Calcium Scoring ®, Siemens, Forchheim, Germany). One experienced observer (A.C.W, 5 or more years of CT coronary angiography training) graded the overall image quality of the best selected CTCA datasets.

A dataset, or the combination of datasets, was classified as good, if no or mild coronary motion was present and the observer was confident in the diagnostic evaluation, or impaired if extensive coronary motion was present and the observer experienced impairment in performing the diagnostic evaluation.

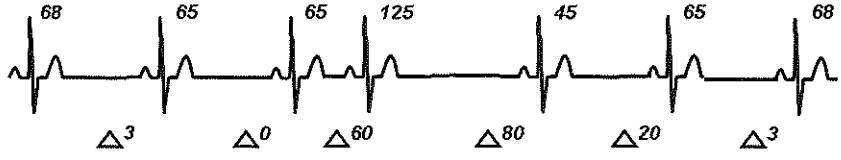
Two experienced observers (A.C.W., N.R.M., 5 or more years of CT coronary angiography training) unaware of the results of CCA, independently scored all CTCA datasets for the pres-

ence of significant stenoses using axial source images, as well as multiplanar or curved reformatted reconstructions and maximum intensity projections. Stenoses were visually classified into significant (≥50% lumen diameter reduction) or non-significant (<50% reduction). Segments distal to a chronic total occlusion were excluded. An intention to diagnose design was used: all scanned patients including all segments were analyzed even if the image quality was impaired. Interobserver disagreements were resolved by consensus in a joint session.

Classification according to heart rate frequency and variability

Patients were categorized into 3 HRF groups: low (≤65 bpm), intermediate (66-79 bpm) and high (≥80 bpm). The absolute difference between two consecutive heart beats was recorded during CTCA. HRV was defined as the sum of these absolute differences divided by the number of heart beats and expressed as mean interbeat difference (IBD, Figure 3). Patients were categorized into 4 HRV groups: normal (0-1 IBD), minor (2-3 IBD), moderate (4-10 IBD) and severe (> 10 IBD).

Figure 3. Schematic Illustration of Heart rate Variability (HRV) Assessment.



The absolute difference (Δ) between two consecutive heart beats was recorded. HRV was expressed as mean interbeat difference (IBD) defined as the sum of these absolute differences (3+0+60+80+20+3) divided by the number of heart beats during CTCA (7) = 448 / 7 = 23

Subanalysis according to Agatston score

A subanalysis on diagnostic performance in patients with low (≤ 100 Agatston score) and high (> 100 Agatston score) was performed and sensitivity, specificity, and positive and negative predictive values among HRF groups and HRV groups were calculated.

Radiation Exposure

The radiation exposure for Dual-source CTCA was quantified by the CTDIvol values obtained from the CT scanner console. The CTDIvol estimates the average dose within the scanned volume based on a standardized phantom (12) and takes the influence of both the ECG-pulsing and the pitch on the dose into account. In order to study solely the effect of ECG-pulsing on the dose, the CTDIw values were calculated [CTDIw = CTDIvol x pitch], which are a measure for radiation dose independent of pitch.

Statistical Analysis

The statistical analyses were performed using SPSS (version 12.1 SPSS Inc., Chicago, Ill, USA.) and STATA (SE 8.2, College Station, Texas, USA).

Categorical patient and scan characteristics were expressed as numbers and percentages and continuous variables were expressed as mean (standard deviation) values. Diagnostic performance of CTCA for the diagnosis of significant CAD compared to the standard of reference QCA on CCA was determined with sensitivity, specificity, positive predictive value, and negative predictive value and their corresponding 95% confidence intervals. The difference in age between males and females was calculated using the student-T test.

The image quality and diagnostic performance according to Agatston scores among HRF groups and among HRV groups were compared using the Fisher exact test and a p-value <0.05 was considered statistically significant. For the dose estimates, the two-way Anova test was performed to evaluate the effect of HRF and HRV on the radiation exposure (CTDIvol and CTDIw) for both fixed ECG pulsing and optimal ECG pulsing windows. A p-value <0.05 was considered statistically significant. Inter-observer variability for the detection of significant stenoses was determined by kappa-statistics. Intra-observer agreement of one observer was determined in a set of 100 patients and presented by kappa-statistics. The data was clustered implying that potential correlation existed between the multiple (seventeen) segments analyzed per patient. To adjust for the clustered nature of the data, sensitivity, specificity, negative and positive predictive values were studied by a bootstrap analysis (13, 14). A total of 1000 replications of the dataset were obtained by sampling segments (with replacement), with the patient as cluster.

RESULTS

Patient and scan characteristics are listed in Table 1. There was no significant difference ($p = 0.33$) in age between males (60.6±11.0 years) and females (59.9±11.1). Mean scan length for the CTCA-protocol was 11.0±3.1 cm. A total of 428 (46%, 428/927) of patients received long-term β-blockers. In patients with moderate HRV (13%, 124/927), 6% (7/124) presented with ventricular extra-systolic beats, 1% (1/124) with atrial fibrillation and 94% (116/124) with mild sinus node arrhythmia. In patients with severe HRV (6%, 52/927), 37% (19/52) presented with ventricular extra-systolic beats, 19% (10/52) with atrial fibrillation, 2% (1/52) with ventricular bigeminy, and 2% (1/52) with ventricular trigeminy, and 40% (21/52) with sinus node arrhythmias.

RADIATION EXPOSURE

Adaptive ECG pulsing was successfully applied in all patients and no cases were excluded due to incorrect timing of the high X-ray tube output. In patients scanned with a fixed ECG pulsing window and 20% tube current reduction outside the ECG pulsing window, mean CTDIvol was significantly ($p <0.05$) lower in high HRF (53.6 mGy) compared to low HRF (73.1 mGy). This dose reduction can be contributed to the increase of pitch values for higher heart rates. The efficacy of ECG-pulsing in this group of patients is significantly ($p <0.001$) influenced by HRF and HRV. However, the impact of HRV and HRF in this group is moderate: the mean CTDIw was only 7% higher in the high HRF group (19.5 mGy) compared to the low HRF group (18.1 mGy), and 12% in the severe HRV group (20.4 mGy) compared to the normal

Table 1. Patient and Scan Characteristics.

	Overall	HRF groups			HRV groups			
		Low ≤65 bpm	Interme-diate 66-79 bpm	High ≥80 bpm	Normal 0-1 IBD	Minor 2-3IBD	Moderate 4-10 IBD	Severe >10 IBD
N	927	423 (46)	333 (36)	171 (18)	372 (40)	379 (41)	124 (13)	52 (6)
Male	600 (65)	319 (75)	193 (58)	88 (51)	251 (67)	239 (63)	76 (61)	34 (65)
Age (yrs)	60.3±11.0	61.5±10.6	61.0±11.4	56.2.0±10.3	61.8±10.6	58.5.±11.0	60.1±11.2	63.7±11.7
Long-term β-blockers	428 (46)	241 (57)	134 (40)	53 (31)	204 (55)	160 (42)	39 (31)	9 (17)
Mean HRF (bpm)	69.1±11.3	57.6±5.5	71.9±3.7	88.8±8.4	66.4±12.7	69.4±11.9	73.0±14.6	67.7±13.9
Mean HRV (IBD)	3.9±8.4	3.2±8.2	3.4±5.7	3.1±3.8	0.9±0.4	2.2±0.5	5.1±1.6	23.3±18.5
Scan parameters								
Pitch ǂ	0.30±0.07	0.25±0.04	0.31±0.05	0.38±0.07	0.29±0.07	0.30±0.07	0.30±0.07	0.26±0.06
Pitch ∓	0.29±0.06	0.25±0.03	0.30±0.04	0.38±0.05	0.27±0.05	0.29±0.06	0.31±0.06	0.25±0.06
Fixed ECG pulsing ǂ	640 (69)	303 (72)	218 (66)	119 (70)	304 (82)	236 (62)	65 (52)	35 (67)
Optimal ECG pulsing ∓	287 (31)	120 (28)	115 (34)	52 (30)	68 (18)	143 (38)	59 (48)	17 (33)
$CTDI_{VOL}$ (mGy) ǂ	65.6±15.1	73.1±13.5	62.0±11.5	53.6±14.4	63.6±13.4	64.7±12.3	69.6±16.6	83.9±19.0
$CTDI_{VOL}$ (mGy) ∓	50.6±16.5	48.3±11.7	56.1±14.0	42.7±16.9	47.1±10.8	47.3±12.1	52.2±19.4	82.3±19.2
$CTDI_{w}$ (mGy) ǂ	18.5±1.7	18.1±1.8	18.7±1.5	19.5±1.4	18.0±1.5	18.7±1.3	19.8±1.9	20.4±1.9
$CTDI_{w}$ (mGy) ∓	14.3±4.3	11.7±3.5	16.6±3.5	14.9±4.1	12.8±3.8	13.7±3.9	15.4±3.9	20.4±2.8

N indicates number; HRF, heart rate frequency; HRV, heart rate variability, ; bpm; IBD, interbeat difference; CCA, conventional coronary angiography; CTDI; computed tomography dose index; ǂ indicates a fixed adaptive ECG pulsing algorithm (ECG pulsing window: 25-70% of R-R interval (all HRF), and reduced exposure to 20% of maximum outside the ECG pulsing window) ∓ indicates optimal adaptive ECG pulsing algorithms (ECG pulsing windows: 60-76% of R-R-interval in HRF ≤ 65 , 30-77% of R-R-interval in HRF 66-79 , 31-47% of R-R-interval in HRF ≥80 , and reduced exposure to 4% of maximum outside the ECG pulsing window)

HRV group (18.0 mGy). The impact on radiation exposure due to HRV within the different groups of HRF was not significantly different ($p = 0.1$). In patients scanned with optimal ECG pulsing windows and 4% tube current reduction outside the ECG pulsing window, differences in CTDIvol between low HRF and high HRF were smaller compared to the corresponding differences in patients scanned with fixed ECG pulsing windows. Both the HRF and HRV have a significant ($p < 0.001$) impact on the efficacy of ECG-pulsing in the group of patients with optimized ECG-pulsing. The mean CTDIw was 30% higher in the intermediate HRF group (16.6 mGy) compared to the low HRF group (11.7 mGy), and 21% higher in the high HRF group (14.9 mGy) compared to the low HRF group. The mean CTDIw was even 37% higher in patients with severe HRV (20.4 mGy) as compared to the normal HRV group (12.8 mGy). We observed a significant difference ($p = 0.01$) on the impact of radiation exposure due to HRV within the different groups of HRF, which can be explained by the relatively low number of patients with both a high HRF and HRV in this group of patients.

Image quality

The best selected datasets yielded good image quality in 98% (910/927) and impaired image quality in 2% (18/927) of patients. Impaired image quality was more frequently found in patients with high HRF (5%, 8/171) compared to intermediate (2%, 8/333) or low (1%, 2/423) HRF, and in patients with severe HRV (10%, 5/52) compared to moderate (7%, 9/124), minor (1%, 3/379), or normal (1%, 1/201) HRV. However, these differences in image quality found among HRF or HRV groups were not statistically different.

Diagnostic performance

The diagnostic performance of CTCA to detect significant coronary artery stenosis according to HRF and HRV are detailed in Table 2 (segment-by-segment and patient-by patient analysis).

The analysis per segment was confirmed by bootstrap analysis. Kappa-values for the inter- and intra-observer variability on a per segment level were 0.70 and 0.73, respectively. In patients with low (≤65 bpm), intermediate (66-79 bpm) and high (≥80 bpm) HRF, sensitivity was 100%, 99%, and 100% on an overall patient-by-patient analysis.

Specificity was 81%, 87%, and 87%; positive predictive value 96%, 94%, and 90%; and negative predictive value 100%, 98% and 100%. In patients with normal (0-1 IBD), minor (2-3 IBD), moderate (4-10 IBD) and severe (>10 IBD) HRV, sensitivity was 100%, 99%, 100%, and 100% on an overall, patient-by-patient analysis. Specificity was 80%, 90%, 83% and 91%; positive predictive value 94%, 96%, 92%, 94%; and negative predictive value 100%, 98%, 100%, and 100%. A subanalysis according to Agatston calcium scores showed no significant differences in sensitivity, specificity, positive and negative predictive value among HRF or HRV groups in patients with low Agatston scores (≤100). However, there was a nonsignificant trend towards a lower specificity (96% vs. 91%) and lower positive predictive value (98% vs. 82%) in patients with low vs. high HRF. A similar trend was observed in patients with normal vs. severe HRV (specificity: 95% vs. 88%; positive predictive value: 95% vs. 88%) (Figure 4). In

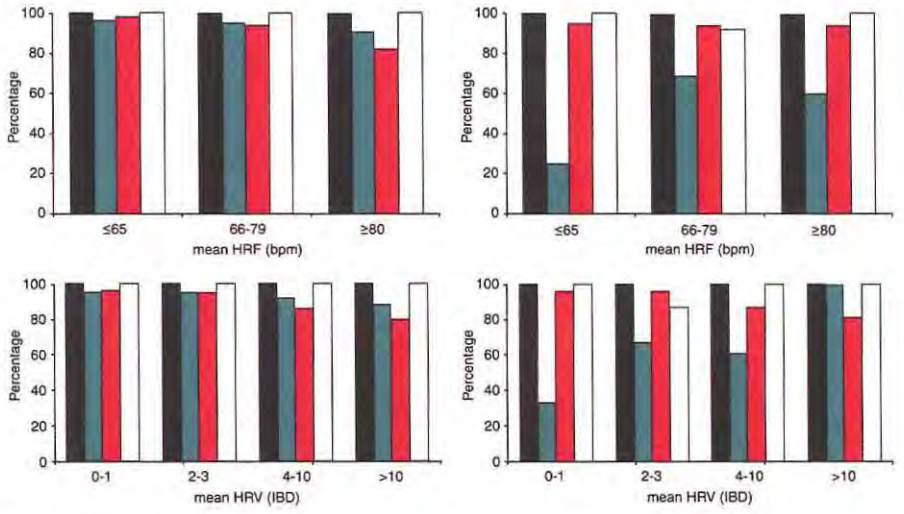
Table 2. Impact of Heart Rate Frequency (HRF) and Heart Rate Variability (HRV) on Diagnostic Performance of Dual-source CTCA to Detect Significant (≥50% lumen diameter reduction) Coronary Artery Stenosis.

	Overall	HRF groups			HRV groups			
		Low ≤65 bpm	Intermediate 66-79 bpm	High ≥80 bpm	Normal 0-1 IBD	Minor 2-3 IBD	Moderate 4-10 IBD	Severe >10 IBD
Patient level								
N	444	189	170	85	201	163	52	28
Prevalence of significant stenosis, %	71	81	69	55	75	71	65	61
Sensitivity, %	100 (98-100)	100 (97-100)	99 (95-100)	100 (91-100)	100 (97-100)	99 (96-100)	100 (87-100)	100 (77-100)
Specificity, %	85 (77-91)	81 (63-91)	87 (74-94)	87 (71-95)	80 (66-90)	90 (77-96)	83 (58-96)	91 (57-100)
PPV, %	94 (91-97)	96 (91-98)	94 (88-97)	90 (87-100)	94 (89-97)	96 (90-98)	92 (77-98)	94 (71-100)
NPV, %	99 (94-100)	100 (85-100)	98 (87-100)	100 (87-100)	100 (89-100)	98 (87-100)	100 (75-100)	100 (66-100)
Segment level								
N	6788	2848	2613	1327	3066	2497	801	424
Prevalence of significant stenosis, %	11	14	10	8	12	11	10	8
Sensitivity, %	95 (93-96)	96 (93-96)	92 (88-95)	96 (90-99)	93 (90-96)	97 (94-98)	96 (89-99)	88 (72-96)
Specificity, %	96 (96-97)	96 (95-96)	97 (96-98)	96 (95-97)	96 (95-97)	96 (96-97)	97 (96-98)	96 (93-97)
PPV, %	76 (73-78)	77 (73-81)	77 (72-81)	69 (61-76)	75 (71-79)	77 (72-81)	80 (71-87)	64 (49-77)
NPV, %	99 (99-100)	99 (99-100)	99 (99-100)	100 (99-100)	99 (99-99)	100 (99-100)	100 (99-100)	99 (97-100)

N indicates number; HRF, heart rate frequency; HRV, heart rate variability; bpm; IBD, interbeat difference; PPV, positive predictive value; NPV, negative predictive value; number between parentheses indicates 95% confidence intervals. Values in parentheses represent upper and lower bound for 95% confidence interval.

patients with high Agatston scores (>100), we did not observe such a trend and diagnostic performance did not correlate to HRV or HRF.

Figure 4. Subanalysis of Diagnostic Performance in Patients with Low (<100) and High (<100) Agatston.

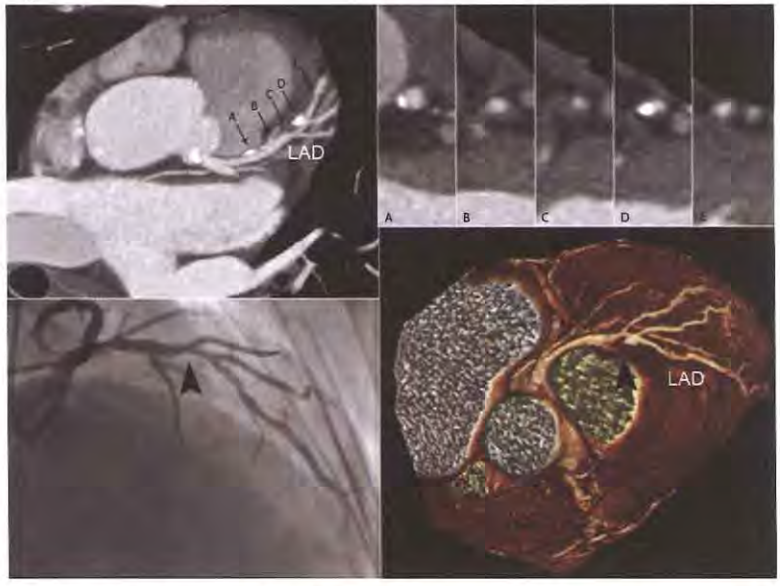


Graphs show subanalysis of diagnostic performance (black = sensitivity, blue = specificity, red = PPV, white = NPV) in patients with low (≤100, upper and lower left) and high (>100, upper and lower right) Agatston scores. bpm = beats per minute.

DISCUSSION

CT coronary angiography has emerged as a reliable tool to detect or rule out significant stenoses in selected patients with regular and preferably low (<65 bpm) heart rates. Beta-blockers are commonly administered prior to CTCA to lower the heart rate, thereby reducing the number of image-degrading motion artifacts. Dual-source CT scanners provide an improved temporal resolution compared to conventional (single-source) CT equipment and may obviate the need for pre-scan beta-blockers (15, 16). Previous small-sized studies demonstrated an increased diagnostic performance of spiral CTCA using dual-source equipment in patients with various HRF. However, the number of included patients with high HRF (>80 bpm) was consistently low, and the vast majority of studies excluded patients with arrhythmias (15-21). Few studies have investigated the impact of heart rate variability on image quality and diagnostic performance. In these studies, HRV was defined as the standard deviation of the mean heart rate during CTCA. However, this definition of HRV may not give accurate insight of the impact of HRV during spiral CTCA; a gradual increase in heart rate frequency does not generally impact on image quality, while the SD of the mean HR may be high. Instead, a sudden

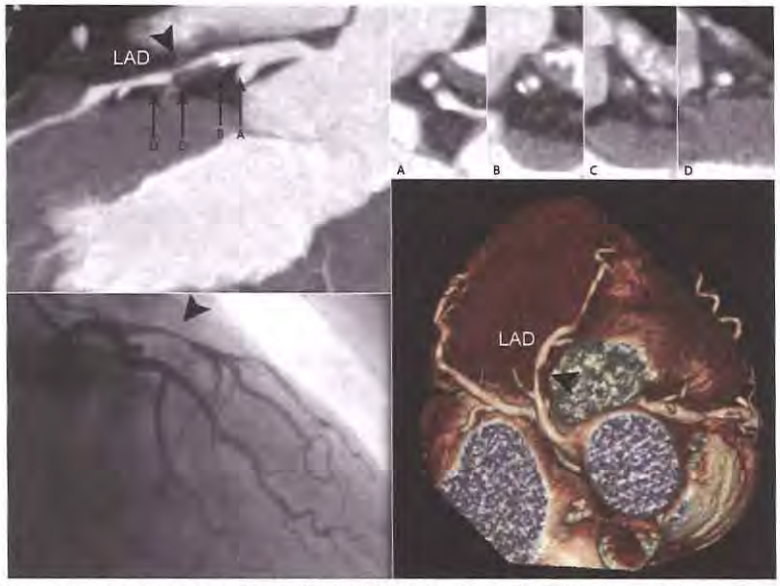
Figure 5.



Coronary angiography in patient with atrial fibrillation with slow ventricle response. CT coronary angiogram (upper left) shows cross-sections of proximal left anterior descending artery (LAD) A–E (upper right). Conventional coronary angiogram (lower left) and volume-rendered reconstruction (lower right) show stenosis (arrowhead).

change in heart rate may cause several problems in the acquisition of spiral CTCA, such as: 1) mis-triggering of the ECG pulsing algorithm resulting in low-dose images at the desired phase of image reconstruction, and 2) artifacts due to differences in image reconstruction phases between consecutive heart beats. Previously, ECG pulsing could not be applied in patients with arrhythmias. The adaptive ECG pulsing algorithm reacts to such a sudden change in R-R interval by switching off the ECG pulsing during subsequent R-R-intervals. We therefore defined HRV as the mean inter-beat difference between 2 consecutive heart beats, and studied the impact of adaptive ECG pulsing on radiation exposure, image quality and diagnostic performance of dual-source CTCA in a large patient population with a wide variety of heart rates. We tested the use of a newly developed, adaptive ECG pulsing algorithm in a large cohort of patients with various HRF and HRV. We observed no patients with impaired image quality on the basis of mis-triggering of the ECG pulsing algorithm, even in patients with severe HRV. This finding indicates that adaptive ECG pulsing is now robust and should be used in all patients undergoing spiral CTCA. However, it should be noted that the dose reduction feature of ECG pulsing is almost completely eliminated in patients with severe HRV, because the ECG pulsing is partly or totally or switched off throughout the scan in patients with arrhythmia to maintain diagnostic image quality. Therefore, the potential benefit of spiral CTCA should be carefully weighed against the risk of developing radiation induced cancer, in particular, in young patients presenting with arrhythmias (22). We found a high overall diagnostic performance of Dual-source CTCA in the

Figure 6.



Coronary angiography in patient with high HRF (84 beats/min). CT coronary angiogram (upper left) shows cross-sections of proximal left anterior descending artery (LAD) A–D (upper right). Conventional coronary angiogram (lower left) and volume-rendered reconstruction (lower right) show stenosis (arrowhead).

detection or exclusion of significant coronary artery stenosis with a sensitivity of 100% and a negative predictive value of 99% on a per patient basis. These results were obtained without exclusion of any segments or patients on the basis of impaired image quality. We found no significant differences in image quality or diagnostic performance among HRF and HRV groups. We only observed a trend towards more 'false positive' results reflected by a lower specificity and positive predictive value in patients with low calcium scores (<100 Agatston score) and HRF ≥80 bpm or HRV >10 IBD. We did not find this trend in patients with higher calcium scores, which indicates that the well known impact of severe coronary calcifications outweighs the limited impact of HRF or HRV on diagnostic performance of CTCA. An important disadvantage of spiral CTCA is its relatively high radiation exposure (3). Recently, sequential or step-and-shoot (SAS) CTCA has gained renewed interest as a scan technique to reduce radiation exposure while preserving diagnostic image quality. However, SAS CTCA is currently limited to selected patients with low and regular heart rates only (23-26). Although this scan mode was not yet available during the inclusion period of our study, we estimated on the basis of heart rate characteristics (low HRF and normal to minor HRV) in our study population (n=927) that SAS CTCA could have been successfully carried out in approximately 38% (355/927) of patients. The majority of these patients (57%, 204/355) were already on long term beta-blockers, and it may be expected that the number of patients suitable for SAS CTCA would significantly increase by the use of pre-scan beta-blockers. However, spiral CTCA still remains the preferred

scan mode in patients with arrhythmias and or fast HRF. Particularly, spiral CTCA can be used as an alternative to the SAS CTCA in patients with contraindications to administration of beta-blockers (e.g. overt heart failure) or in patients with insufficient decrease of HRF (<65 bpm) despite the use of pre-scan beta-blockers.

LIMITATIONS

In our study, arrhythmic patients were not excluded from CTCA with the exception of a small number (n=6) of patients with atrial fibrillation with fast ventricle response and inclusion of these patients would most likely result in a lower diagnostic performance of dual-source CTCA. We believe that dual-source CTCA is not yet ready for clinical use in these specific patients, because of the occurrence of severe motion artifacts despite the improved temporal resolution of dual-source CT scanners. Future developments such as complete data acquisition during a single heart beat combined with a further increase in temporal resolution of e.g. 25 ms may result in a true heart rate independent image acquisition, even in patients with severe arrhythmia.

CONCLUSION

The use of adaptive ECG pulsing at Dual-source spiral CT coronary angiography provides diagnostic image quality and reliable detection and rule out of obstructive coronary artery disease independent of heart rate frequency or heart rate variability at the cost of a limited dose reduction in arrhythmic patients.

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PART 5

A CURRENT AND FUTURE PERSPECTIVE ON CT CORONARY ANGIOGRAPHY

CHAPTER 12

THE ROLE OF MULTI-SLICE COMPUTED TOMOGRAPHY IN STABLE ANGINA MANAGEMENT - A CURRENT PERSPECTIVE -

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Annick C. Weustink
Pim J. de Feyter

INTRODUCTION

Stable angina is a common and disabling disease, and occurs when there is regional myocardial ischemia caused by inadequate coronary perfusion due to chronic coronary obstruction. Despite the fact that William Heberden already in 1768 gave a clear description of stable angina, the optimal strategy for diagnosis in stable angina is still evolving and there is a variety of non-invasive and invasive tests available. Traditionally ischemic testing includes exercise ECG and stress myocardial perfusion imaging techniques for the non-invasive identification of inducible ischemia, but non-invasive anatomic testing is emerging. Invasive coronary angiography (ICA) is generally considered the standard of reference for the detection of significant coronary artery stenosis.

Multi-slice CT (MSCT) has rapidly evolved as an alternative imaging test because of its non-invasive nature and high diagnostic performance. Cardiac CT has two modes: a) non-contrast enhanced CT to detect and quantify coronary calcium and b) contrast-enhanced CT to detect non-obstructive and obstructive coronary atherosclerosis. Coronary calcium is considered a proven marker of the presence of atherosclerosis and the prognostic value of coronary calcium scoring is independent and incremental to the predictive value of traditional risk factors (1). Remarkable advances in MSCT technology have been achieved with successive CT scanner generations. The current state-of-the-art 64 slice CT scanners, necessary for contrast-enhanced CT coronary angiography (CTCA), provides high-definition images of coronary non-obstructive and obstructive atherosclerosis, with characterization of coronary plaques into calcific and non-calcific components (2-4).

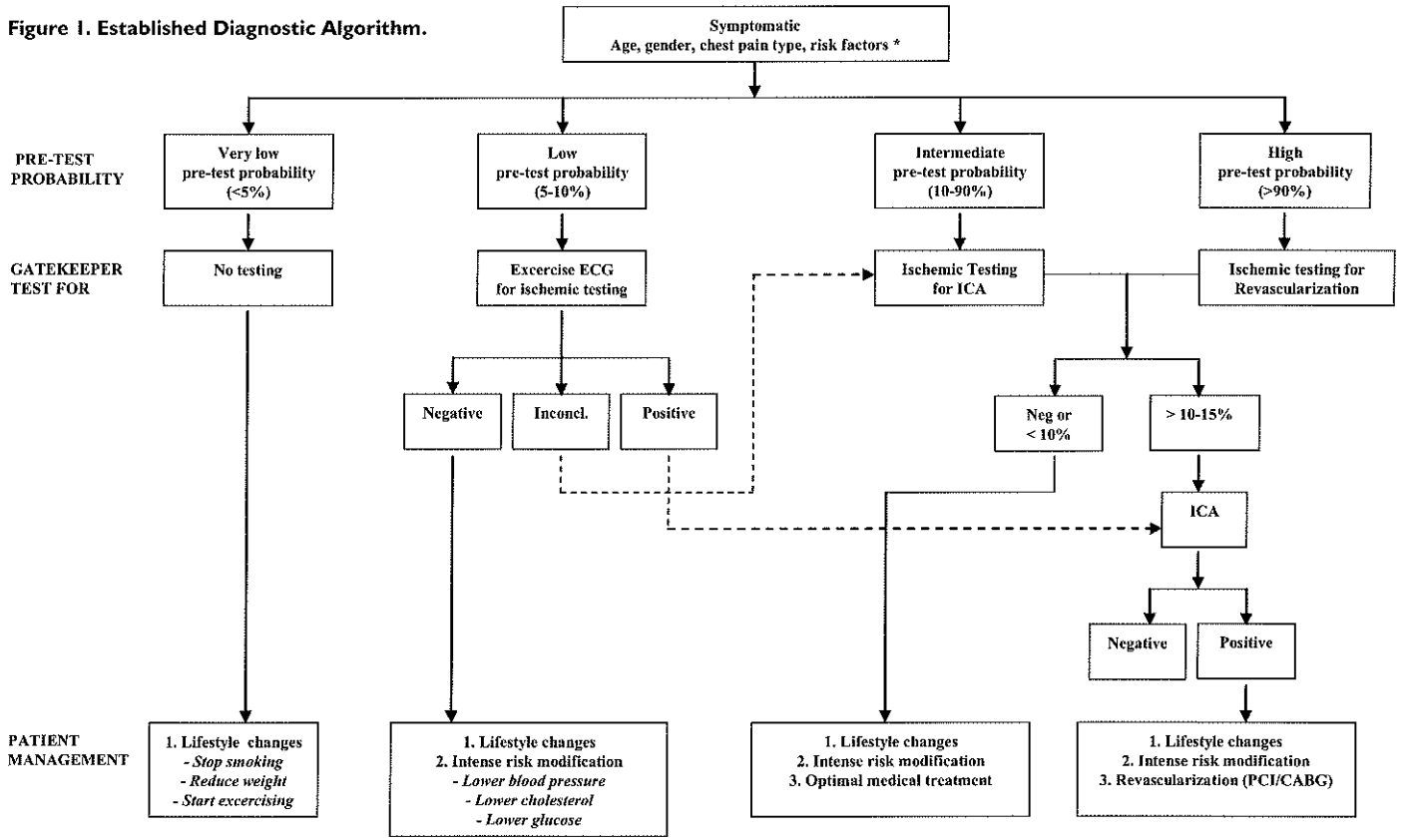
Despite the growing use of MSCT, its clinical utility in the hierarchy of coronary investigations remains to be established. There is an ongoing debate whether management of patients with stable angina should be primarily based on anatomical or functional testing. Notably, there is a well known dissociation between the functional relevance of a coronary obstruction (ischemia) and the severity of a coronary obstruction that is haemodynamically significant (5, 6).

This report provides a current perspective on the potential role of MSCT in patients presenting with stable angina. We propose an alternative diagnostic testing algorithm using MSCT for the management of stable angina, and discuss limitations and future directions of CTCA.

CURRENT DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH STABLE ANGINA

The current diagnostic work-up of patients with stable angina is based on the outcome of clinical evaluation, assessment of ischemia and subsequent management taking into account prognosis and effectiveness of medical and revascularization therapy (7, 8).

Figure 1. Established Diagnostic Algorithm.

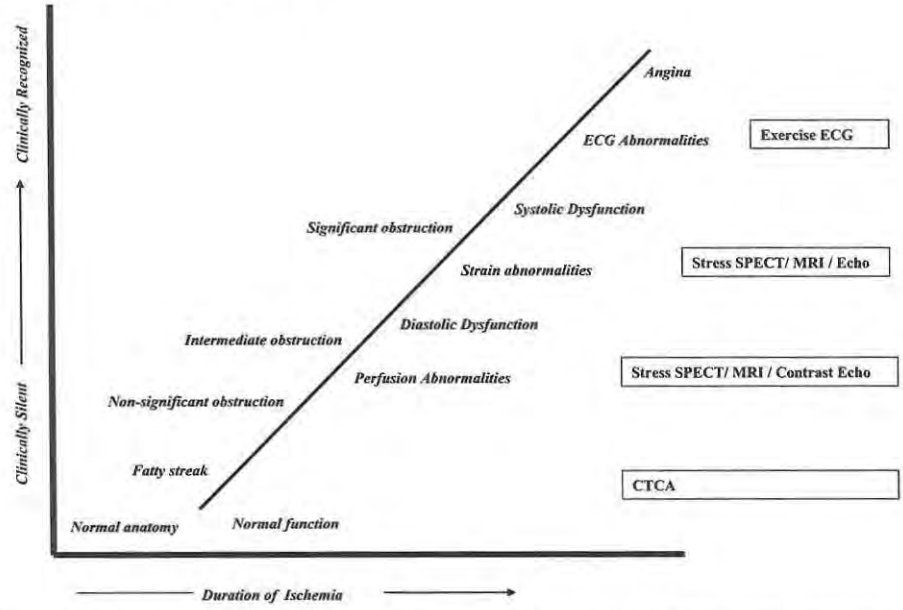


* If risk factor diabetes or hypertension present, patients are categorized to high pretest probability category. CTCA: computed tomography coronary angiography; ECG: electrocardiography; ICA: invasive coronary angiography. Ischemic testing includes stress myocardial perfusion imaging; SPECT or single photon emission computed tomography [relative flow], PET or positron emission tomography [absolute flow], MRI or magnetic resonance imaging [flow reserve], stress echocardiography [wall motion].

Clinical evaluation includes age, gender, history of chest pain, weight, blood pressure, ECG and laboratory tests of glucose and total cholesterol.

History of chest pain allows classification into A) typical angina that meets the following characteristics 1) substernal chest discomfort 2) provoked by exertion or emotional stress and 3) relieved by rest or nitroglycerine. B) atypical angina that meets 2 of the above characteristics and C) non-anginal chest pain that meets only one or none of these characteristics.

Figure 2. The Ischemic Cascade.



Myocardial dysfunction occurs in a predictable sequence of events which is detectable prior to clinical symptoms.

The clinical evaluation is derived from simple easy obtainable variables and is used as the initial step in the diagnosis and management of patients with stable angina to categorize these patients into a low, intermediate or high pretest probability group.

The pretest probability categorization is important because 1) it has a significant impact on the posttest probability of disease 2) the prognosis and management of patients is different in each category 3) the selection of a diagnostic test depends on the consequences this may have on the 2 above considerations.

Based on the above considerations and in agreement with the guidelines, a frequently used diagnostic algorithm is presented (Figure 1). This algorithm is an oversimplification of the sometimes complex clinical situation of patients presenting with stable angina and follows 3 steps: 1) pretest probability assessment 2) selection of a diagnostic test and 3) subsequent patient management. The pretest probability of the presence of obstructive CAD can be estimated using prediction score algorithms devised by Diamond and Forrester or Duke Clinical Score using the variables from the clinical evaluation (9, 10). There is no consensus as to the exact range of pretest likelihood classification into low, intermediate or high pretest risk, and we have chosen for a very low (<5%), low (5-10%), intermediate (10-90%), and high (>90%) pretest risk (11).

Cardiac diagnostic tests reveal the presence of myocardial ischemia shown as presence of electrocardiographic ST segment depression, myocardial perfusion defects or induced wall motion abnormalities. The ischemic cascade demonstrates the sequence of abnormalities that occur during ischemia (Figure 2). Perfusion abnormalities are the earliest manifestation of coronary ischemia that can be detected by highly sensitive tests such as SPECT/MRI/contrast echocardiography, followed by systolic dysfunction and associated stress-induced motion abnormalities, then ECG abnormalities as a later manifestation of ischemia and finally angina (12). The diagnostic accuracy of the various tests is summarized in Table 1.

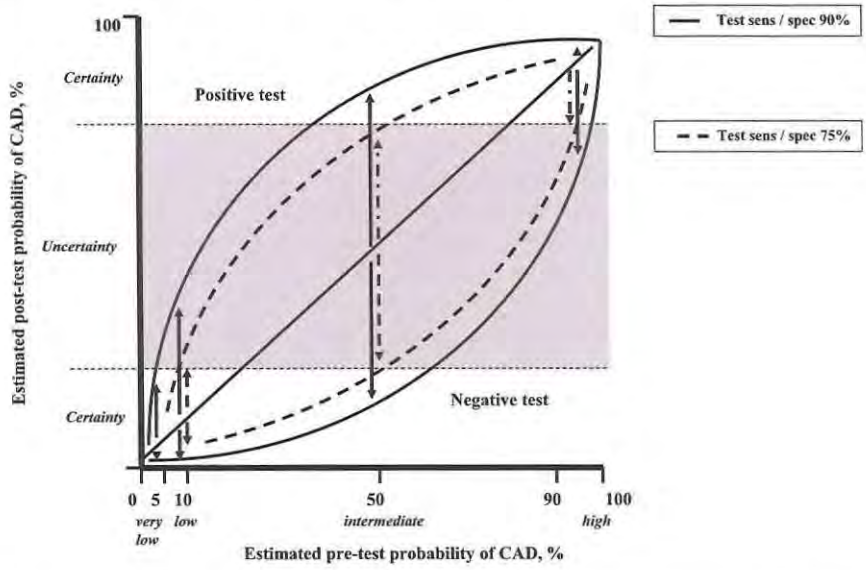
The posttest probability of CAD depends on the pretest risk and the sensitivity and specificity of the test (9, 10). The selection of a test depends predominately on the diagnostic accuracy of the test, but also other factors may play a role including safety, costs, availability, patient's convenience and the use of radiation. No test is perfect and the goal of a test is to provide a level of certainty indicating the presence or absence of CAD (Figure 3). The level of certainty is arbitrary and depends on the estimated prognosis of patients with a "missed" diagnosis or whether additional testing is able to further improve the level of certainty allowing better patient decision management. Thus, a test may serve as a gatekeeper for additional testing, while a functional test also may be useful to make a decision regarding medical or revascularization treatment. At the very low end of the likelihood spectrum no testing is required. Patients with low pretest probability may undergo the inexpensive, widely available bicycle ECG stress test. Patients with intermediate pretest probability are referred for functional testing to assess the presence and extent of myocardial ischemia to guide decision for medical treatment. Patients at high risk do not require testing to confirm the presence of the high likelihood of CAD but require testing to assess the extent of ischemia to guide the decision for revascularization.

Patient management following clinical evaluation, pretest risk classification and outcome of selected testing is based on the presence of modifiable (smoking, obesity, exercise) or treatable risk factors (blood pressure, cholesterol, glucose), on the presence of mild to moderate extent of ischemia requiring medical treatment or large extent of ischemia where revascularization has shown to reduce the extent of ischemia and improve prognosis (13, 14).

Table 1. The Diagnostic Performance of Non-invasive Cardiac Tests for the Diagnosis of CAD (12).

	Sensitivity (%)	Specificity (%)
Exercise ECG	65-70	70-75
Exercise stress echocardiography	80-85	80-85
Dobutamine stress echo	80-85	85-90
Exercise myocardial perfusion SPECT	85-90	85-90
Pharnacologic myocardial perfusion SPECT	80-90	80-90

Figure 3. Relation between Pre- and Posttest Probability.



Diagnostic accuracy improves with a test with a higher sensitivity and specificity. Bayesian theory has shown that the value of non-invasive testing is greatest in patients with an intermediate pretest probability of having CAD.

Assume certainty level.

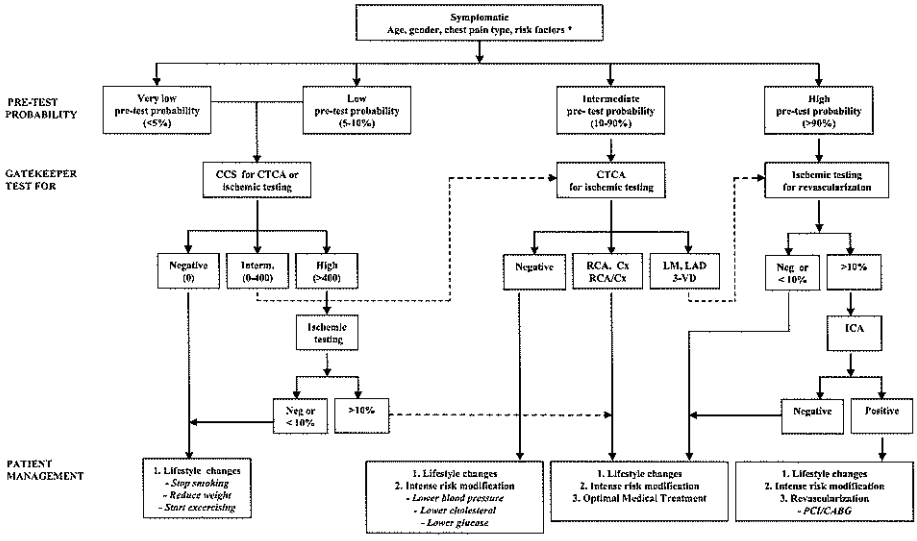
Very low pretest probability (<5%): uncertainty will not be achieved.

Low pretest probability (5-10%): only certainty with a negative test result.

Intermediate pretest probability: (10-90%): certainty with a negative and positive test result.

High pretest probability: (>90%): only certainty with a positive test result.

Figure 4. Alternative Diagnostic Algorithm.



* If risk factor diabetes or hypertension present, patients are categorized to high pretest probability category. CCS: coronary calcium score (expressed as Agatston Score), CTCA: computed tomography coronary angiography, ICA: invasive coronary angiography, RCA: right coronary artery, Cx: left circumflex artery, LM: left main, LAD: left anterior descending artery, 3-VD: 3-vessel disease. Ischemic testing includes stress myocardial perfusion imaging: SPECT or single photon emission computed tomography [relative flow], PET or positron emission tomography [absolute flow], MRI or magnetic resonance imaging [flow reserve]; stress echocardiography [wall motion]

ROLE OF MULTI-SLICE COMPUTED TOMOGRAPHY IN THE DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH STABLE ANGINA

So far, non-invasive tests, assessing the presence of coronary obstructions were based upon the detection of myocardial ischemia caused by coronary flow limiting stenosis. These tests were predominately used as "gatekeeper" for invasive coronary angiography, the anatomical counterpart of myocardial perfusion abnormalities, because invasive coronary angiography is expensive, patient-unfriendly and in few cases associated with complications (15).

The introduction of CTCA may cause a shift in the current paradigm of the diagnostic work-up of patients with stable angina, because the non-invasive nature of this imaging modality may decrease the threshold to refer patients to establish the anatomical presence of coronary atherosclerotic obstruction (Figure 4).

The presence of coronary calcium, as assessed by non-contrast enhanced CT, is a marker of the presence of coronary atherosclerosis (1), but its presence does not necessarily imply the

presence of a significant coronary obstruction. There is a direct relation between the magnitude of the coronary calcium score and the presence of a coronary obstruction, which is located anywhere in the coronary tree and not necessarily at the site calcific plaque (16) (17). The absence of coronary calcium does not completely exclude the presence of coronary atherosclerosis, and in a few cases non-calcified plaques, although these are mostly nonobstructive, are present (18). The absence of coronary calcium is associated with a very low risk of adverse coronary events (19).

Coronary calcium scoring may be useful as an initial, reliable gatekeeper for ischemic testing in patients with a very low and low pretest probability of CAD (Figure 4). The use of the coronary calcium score is acceptable because it is patient-friendly and inexpensive, lack of use of contrast but associated with, albeit, low radiation exposure (< 1 mSv).

The presence of extensive coronary calcium seriously limits the reliability of CTCA and consequently in patients with a high coronary calcium score (Agatston >400) an ischemic test would be more effective than a CTCA (Figure 4).

The presence of obstructive coronary atherosclerosis is assessed by contrast-enhanced CTCA. The diagnostic performance of CTCA has been extensively investigated in patients with intermediate and high pretest probability by comparing the diagnostic accuracy of 64-slice CTCA to the gold standard invasive coronary angiography [Table 2 and 3]. The very high negative predictive value is outperforming any other test and strongly supports the use of CTCA as reliable gatekeeper to invasive coronary angiography, in particular, in patients at intermediate risk (20).

An alternative approach to the established diagnostic algorithm in patients with low to intermediate pretest risk is the use of coronary CTCA as the initial test (Figure 4). A negative CTCA is highly reliable to exclude disease and is associated with an excellent short to intermediate prognosis (21-24). The positive predictive value of CTCA to detect a significant coronary obstruction is only moderate and it is recommended to perform an ischemia test in patients who according to CTCA have left main and/or 3-vessel disease, which is associated with an adverse prognosis that may be improved by revascularization (25). In patients with a high pretest probability the question is one of prognosis and benefit from revascularization rather than diagnosis and an initial functional test should assess the presence and extent of ischemia to guide to medical treatment or referral to invasive coronary angiography and revascularization.

LIMITATIONS OF CTCA

The limitations of CTCA, despite remarkable technical developments, are fivefold and include 1) calcification blooming artefacts 2) limited spatial and temporal resolution 3) unpredictability of haemodynamic significance of intermediate coronary lesions 4) radiation exposure and 5) difficulties to acquire motion-free, high-quality images in patients with arrhythmias.

Coronary calcifications cause blooming artefacts of coronary calcific lesions which either obscure adequate evaluation of the underlying coronary lumen or induce an overestimation of the severity of a coronary obstruction. Both problems result in limitations of the diagnostic performance of CTCA and even the introduction of newly developed CT-technology with improved spatial resolution or use of dual-energy CT may not fully reduce this problem.

The spatial and temporal resolution of current CT technology falls short of the resolution obtained with invasive coronary angiography. This becomes particularly apparent in the diagnostic performance of smaller parts of the coronary tree, distal segments and side branches, where the sensitivity is approximately 79% as compared to over 90% in the proximal and mid coronary segments (26). Motion artefacts, in particular in the RCA, are still present due to limited temporal resolution of CTCA.

The combination of calcifications and limited resolution results in a rather high number of false positive outcomes, which become predominantly apparent when the diagnostic accuracy is calculated on a segment-based analysis (Table 3) and therefore as of yet cannot replace invasive coronary angiography, which requires precise anatomical delineation of coronary obstructions prior to PCI or CABG.

New CT technology with faster and more sensitive detectors using gemstone technology, and introduction of iterative reconstruction algorithms may further improve spatial resolution. Dual energy CT may be helpful to more precisely characterize plaque components (27) and temporal resolution may be further improved by building CT configurations with more X-ray tubes.

The unpredictability of the hemodynamic significance of CT intermediate coronary lesions raises issues as to the referral for coronary revascularization (PCI or CABG) which is deemed necessary if there is objective evidence of moderate to severe myocardial ischemia (28, 29). Therefore it is recommended to perform a myocardial perfusion challenge following a CT scan with an intermediate lesion. Hybrid imaging with PET-CT and SPECT-CT integrating both functional and anatomic information has, in a few preliminary studies, shown that this yields a better diagnostic performance than stand-alone CT, SPECT or PET (30-33).

The radiation exposure, and the associated increased lifetime risk of cancer and mortality, in particular in younger individuals and women, is of concern (34, 35). Increased awareness among radiologists, cardiologists and technicians should reduce the radiation exposure by using the newest CT-technology which allows tailored CT protocols with use of prospective CT scanning (36, 37). Unnecessary CT scanning must be avoided. Institution of these measures has significantly reduced the effective dose to less than 4 mSv and with the use of the latest Flash CT-scanner to approximately 1 mSv (38).

The use of 320-row CT scanner, allowing whole-heart imaging in one heart beat, may resolve arrhythmia issues, and result in motion-free coronary imaging (39, 40).

FUTURE

The role of CTCA in the diagnosis and management of patients with stable angina is not firmly established. So far, numerous studies have evaluated the diagnostic performance of CTCA compared to invasive coronary angiography. The majority were single-center studies performed by experienced investigators which probably resulted in better outcomes than may be expected from less experienced centers, which was already apparent in the lesser outcomes of the published 3 multi-center studies (41-43).

In addition, CTCA studies were performed in selected patients referred for invasive coronary angiography thereby introducing a referral bias. The spectrum of patients with stable chest pain is much broader and includes also patients in whom invasive coronary angiography is not deemed necessary, but in whom CTCA as a noninvasive, patient convenient imaging modality may play a diagnostic role. Investigating only patients with a positive CT scan for invasive coronary angiography, while not investigating patients with a negative CT scan in whom referral to invasive coronary angiography is deemed unethical, introduces a verification bias.

These dilemmas can be resolved by not using invasive coronary angiography as a surrogate comparison but instead a randomized trial of a strategy with CTCA and CT-derived clinical management decisions compared to a standard of care strategy with functional testing and its derived clinical management decisions using clinical end-points as primary outcome and cost-effectiveness as secondary end-points.

These randomized studies should provide adequate evidence, according to general accepted rigorous criteria, that CTCA as an alternative to existing functional tests may offer better patient outcome and/or may be cost-effective.

CONCLUSIONS

CTCA has evolved as a reliable alternative imaging modality technique and may be the preferred initial diagnostic test in patients with stable angina with intermediate pretest probability of CAD. However, because CTCA is moderately predictive for indicating the functional significance of a lesion, the combination of anatomic and functional imaging will become increasingly important. The technology will continue to improve with better spatial and temporal resolution at low radiation exposure, and CTCA may eventually replace invasive coronary angiography. The establishment of the precise role of CTCA in the diagnosis and management of patients with stable angina requires high quality randomized study designs with clinical outcomes as a primary outcome.

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CHAPTER 13

FUTURE DIRECTIONS OF CT CORONARY ANGIOGRAPHY

Annick C. Weustink

FUTURE DIRECTIONS OF CT CORONARY ANGIOGRAPHY

CT coronary angiography (CTCA) has rapidly emerged as noninvasive anatomical imaging technique for the detection of signficant coronary artery disease (CAD). ICA is still considered the gold standard for the detection of significant stenosis and is required for the assessment of suitability for revascularization and selection of treatments with percutaneous coronary intervention or coronary artery bypass surgery (CABG). To date, CTCA cannot replace traditional luminology by invasive coronary angiography (ICA), which would require improvement in image quality to provide detailed coronary anatomical information to guide PCI treatment or refer to CABG. Despite remarkable technical developments with succesive generation of multi-slice CT scanners, there are important limitations of the technique that need to be resolved.

The most important drawback of current state-of-the-art CT scanners is the limited spatial resolution. The presence of calcium, metal stents and devices induce blooming artefacts that obscure the coronary lumen. The introduction of iterative image reconstruction algorithms results in improved signal-to-noise ratio and consequenlty lower patient dose (1). The development of more sensitive detectors with faster responses may further improve spatial resolution.

Much improvement in temporal resolution has been achieved with the introduction of dual-source CT scanners. However, temporal resolution is still limited in patients with severe arrythmias resulting in blurred low-quality images. Optimization of electrocardiographic (ECG) guided data acquistion and image reconstruction algorithms may permit reliable diagnosis by CTCA in a wider range of patients. Further expansion of the number of X-ray sources may, if technical feasible, further increase temporal resolution.

The radiation exposure associated with CTCA was relative high (10-20 mSv) with early generation 64-slice CT scanners (2). The application of optimal ECG pulsing and prospective ECG triggering has significantly reduced patient dose to comparable values measured in conventional ICA (3-10 mSv). The latest high-pitch dual-source CT scanners now allow for very low dose (< 1 mSv) CTCA, however, only in selective patient populations.

The unpredictability of haemodynamic relevance of intermediate coronary lesions by CTCA represents another important limitation. According to the practice guidelines, revascularization is best reserved for stable patients with moderate to severe objective evidence of ischemia (3). Newer generation CT scanners including CT scanners with larger (128-, 256-, 320-slice) detector panels, dual-source CT scanners with high-pitch spiral data acquisition, and hybrid CT-SPECT and PET-CT scanners provide not only anatomical but also functional quantitative information. First-pass enhancement of the myocardium is now feasible to determine the hemodynamic relevance of intermediate coronary lesions (1). Dual-energy data acquisition results in increased tissue-contrast allowing more precise assessment of first-pass contrast perfusion disturbance in significant coronary stenosis (1). Molecular PET-CT imaging represents a new application that aims at potential diagnosis and subsequent treatment of the inflammatory processes of CAD (5).

Despite the abovementioned limitations, CTCA offers important new additional information compared to traditional luminology including;

1) distinction between non-obstructive and obstructive coronary stenosis
2) differentation of coronary plaque composition into noncalcified, mixed and calcified plaque.
3) distribution of coronary plaque throughout the coronary tree.

Plaque extent, location and composition are independent predictors of objective ischemia and may represent prognostic cardiovascular risk markers (6,7). With the advent of low-dose scan protocols, CTCA has become more acceptable in asymptomatic at-risk populations and its potential for early risk stratification is currently under investigation. Preliminary data indicate that CTCA has incremental value, independent of age, gender, conventional risk factors and coronary calcium scoring, over the Framingham Risk Score in the prediction of major cardiac events, cardiac mortality and all-cause mortality (8,9,10,11). Notably, a negative CTCA indicates a very low risk of death at short-term follow-up (10,11). There is early evidence that serial CTCA may effectively monitor cardiovascular therapy in high risk asymptomatic patients (4). It is likely that the use of CTCA will continue to expand, particularly in asymptomatic patients with a high likelihood of CAD that can, so far, only noninvasively be detected or excluded by CTCA and may by serial CT imaging provide insights into the natural history of coronary artery atherosclerosis.

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PART 6

SUMMARY AND CONCLUSIONS

CHAPTER 14

SUMMARY AND CONCLUSIONS

DIAGNOSTIC PERFORMANCE OF CT CORONARY ANGIOGRAPHY (PART 2)

CHAPTER 2

Cardiac motion artifacts may decrease coronary image quality with use of earlier CT scanners that have a limited temporal resolution. The dual-source CT scanner is equipped with two X-ray sources and can obtain a higher temporal resolution during image acquisition than single tube scanners, enabling good image quality at higher heart rates. We performed dual-source CT computed tomography (CTCA) in patients referred for invasive coronary angiography (ICA) without the use of pre-scan beta-blockers. No patients or segments were excluded because of impaired image quality due to either coronary motion or calcifications. Sensitivity, specificity and the negative predictive value (NPV) of dual-source CTCA were all >95%. Positive predictive value (PPV) was lower (75%), due to overgrading of segments with calcified plaque. In conclusion, dual-source CTCA is highly sensitive to detect and to reliably rule out the presence of a significant coronary stenosis, even without the use of pre-scan beta-blockers.

CHAPTER 3

In a large single center study, we assessed the diagnostic performance of 64-slice CTCA to detect significant coronary artery disease (CAD) and compared the differences in diagnostic accuracy for men and women in 402 symptomatic patients. The sensitivity and NPV to detect significant CAD were very good, both for men and women; whereas specificity and PPV were lower in women. The per-segment analysis demonstrated lower sensitivity in women compared to men. The sensitivity in women did not show a difference in proximal and mid segments, but was significantly lower in distal segments and side branches.

CHAPTER 4

Assessment of bypass grafts and distal runoffs by ICA is cumbersome and often requires extra procedure time, contrast load, and radiation exposure. We evaluated the contribution of dual-source CTCA in the comprehensive assessment of symptomatic patients after coronary artery bypass grafting (CABG). We observed a 100% sensitivity on a per-segment level for the detection of significant obstructive graft disease and a 95% sensitivity for the detection of significant lesions in distal runoffs. In patients with higher heart rates, specificity and positive predictive value were only 88% and 81% for the native coronary arteries. We concluded that CTCA should not be considered as a substitute for, but rather as complementary to ICA in the diagnostic work-up of symptomatic post-CABG patients, whereas ICA is still required to confirm or refute CT evaluation of obstructive native CAD.

CHAPTER 5

The detection as well as the exclusion of in-stent restenosis can be very challenging. Metal stents have hyperdense struts attenuating the X-ray beam and obscuring the visualisation of the in-stent lumen. We investigated the diagnostic performance of CTCA in the detection of in-stent restenosis in symptomatic patients referred for ICA. Sensitivity, specificity, PPV and NPV, calculated in all stents, were 94%, 92%, 77% and 98%, respectively. In stents with a diameter

of <3 mm, specificity was low (64%). This study showed that in patients with recurrent chest pain after stent implantation, dual-source CTCA performs well in the detection of in-stent restenosis. Stent diameter was a strong predictor for diagnostic performance, with higher false positive findings in the evaluation of smaller stents. The high NPV allows reliable rule out of in-stent restenosis irrespective of stent size.

CLINICAL APPLICATION OF CT CORONARY ANGIOGRAPHY (PART 3)

CHAPTER 6

We compared the diagnostic performance of exercise bicycle testing with CTCA in 334 stable patients, and single-photon emission computed tomography (SPECT) with CTCA in 61 stable patients for the detection of obstructive CAD. The diagnostic performance of exercise bicycle testing was significantly lower, compared to CTCA: sensitivity of 76% vs. 100%; specificity of 47% vs. 74%; positive predictive value 70% vs. 91%; and negative predictive value 30% vs. 99%. In patients who underwent SPECT, a significant difference was found for sensitivity, but not for specificity between SPECT and CTCA. Sensitivity was 89% and 98% for SPECT and CTCA, respectively. Specificity was 77% and 82% for SPECT and CTCA, respectively. In conclusion, SPECT and 64-slice CTCA yielded high diagnostic performance and are superior to traditional exercise bicycle testing for the detection and rule out of obstructive CAD in patients with stable angina.

CHAPTER 7

The clinical utility of a test does not only depend on its diagnostic accuracy, but also on whether the probability of disease after testing improves clear clinical decision making. Because the diagnostic accuracy of a test may differ from its clinical utility in patients with various pretest probabilities of CAD, we examined both stress testing and CTCA in patients with low, intermediate, and high pretest probabilities of CAD. Our findings suggest that an initial stress test might be considered as a first-line test in patients with a low pretest probability of disease, because stress testing is safe, widely available, inexpensive, and—unlike CTCA—does not use ionizing radiation. CTCA was a reliable first-line diagnostic test in patients with an intermediate pretest probability because, unlike stress testing, CTCA yielded sufficient certainty in patients in this group to stop testing or proceed with ICA. In the high pretest probability group, the Duke clinical score provided sufficient certainty (>90%) to proceed with ICA without further noninvasive testing. However, patients in this group often require revascularization, and functional stress testing may therefore still be useful to provide objective evidence of ischemia before revascularization.

Chapter 8

CTCA should not be used indiscriminately because it is associated with exposure of radiation, contrast use and costs. There is increasing evidence that CTCA may be most valuable in patients at intermediate risk of having obstructive CAD. We developed a clinical probability score based on clinical evaluation, bicycle stress testing and CCS to identify patients with stable angina and a positive CTCA. We validated this risk score in an independent patient cohort. We used this risk score to classify patients at low or high pretest risk in whom CTCA would not add diagnostic information and determined the proportion of patients at intermediate pretest risk in whom CTCA was deemed clinically useful. The application of the clinical probability score, using a pretest probability threshold of 20-80%, reduced the initial number of patients to 26% at intermediate risk, while 34% of the patients were classified at low (<20%) pretest risk and 40% at high (>80%) pretest risk. Our results indicate that the risk score is a reliable indicator for restrictive referral to CTCA and may substantially reduce the number of CTCAs that yield no useful information for clinical decision making.

Radiation exposure associated with CT coronary angiography (part 4)

Chapter 9

Radiation exposure to the patient may be substantial in CTCA. ECG-controlled X-ray tube current modulation or 'ECG-pulsing' is an effective tool to reduce patient dose. A dedicated ECG pulsing protocol was designed for dual-source spiral CTCA in 301 patients. We found that the optimal phase of image reconstruction within the cardiac cycle strongly depends on the heart rate of the patient. Our results suggest that, with an optimized ECG pulsing strategy, radiation exposure can be greatly reduced (up to 41%) while preserving image quality, particularly in patients with low or high heart rates. The use of a reduced tube current outside the ECG pulsing window of 4% instead of 20% would have resulted in a further dose reduction of 38%, 9% and 41% in patients with low, intermediate and high heart rates, respectively.

Chapter 10

We evaluated the effects of standard and optimal ECG pulsing protocols on diagnostic performance, radiation dose, and cancer risk in 436 symptomatic patients. Optimal ECG pulsing resulted in a 43% overall reduction in mean effective dose and cancer risk compared with a nonpulsing protocol and a 25% overall reduction in mean effective dose compared with the standard pulsing protocol. Compared with a nonpulsing protocol, optimal ECG pulsing resulted in significant reductions in patient radiation dose and cancer risk (up to 55% reduction in patients with high heart rates) while preserving the diagnostic performance of dual-source CTCA.

CHAPTER 11

Adaptive ECG-pulsing algorithms are able to detect ectopic heart beats and the X-ray tube current modulation is automatically switched off until the heart rate is stable again. Such adaptive ECG-pulsing algorithms in spiral CT are designed to maintain diagnostic image quality in arrhythmic patients. We evaluated the impact of heart rate frequency (HRF) and heart rate variability (HRV) on radiation exposure, image quality and diagnostic performance in a large cohort of patients undergoing dual-source CTCA using adaptive ECG-pulsing. Radiation exposure was significantly higher in patients with low compared to high HRF, and in patients with severe compared to normal HRV. No significant differences among HRF and HRV groups in image quality and diagnostic performance were found. We observed a trend towards a lower specificity (91% vs. 96%) and positive predictive value (82% vs. 98%) in patients with a high HRF or severe HRV as compared to low HRF or normal HRV in patients with a low calcium score.

CURRENT AND FUTURE PERSPECTIVE ON CT CORONARY ANGIOGRAPHY (PART 5)

CHAPTER 12

Based on clinical experience and performed studies, an alternative diagnostic testing algorithm using CTCA for the management of stable angina is presented taken into account the pretest probability of CAD and diagnostic performance of available diagnostic tests.

CHAPTER 13

Future directions of CTCA are discussed.

SAMENVATTING EN CONCLUSIES

DIAGNOSTISCHE ACCURAATHEID VAN CT CORONAIR ANGIOGRAFIE (DEEL 2)

HOOFDSTUK 2

De temporele resolutie van eerste generatie CT scanners bleek onvoldoende voor het vervaardigen van scherpe afbeeldingen van de snel bewegende kransslagvaten. Dual-source CT scanners, uitgerust met twee röntgenbuizen en twee detectoren, resulteerden in een verdere verbetering van de temporele resolutie en maakten snellere beeldacquisitie mogelijk. In het bijzonder werd een hogere beeldkwaliteit verkregen bij patiënten met hogere hartslagen zonder gebruik te maken van hartfrequentie verlagende medicatie voorafgaande aan de scan. Patiënten ondergingen dual-source CT coronair angiografie voorafgaande aan het invasieve coronair angiogram en de diagnostische accuraatheid van beide technieken voor het opsporen van significante vernauwingen (>50% lumen reductie) in de kransslagvaten werd vergeleken. Er werden geen coronair segmenten uitgesloten van evaluatie op basis van de beeldkwaliteit, die mogelijk verstoord kon zijn door de aanwezigheid van bewegingsartefacten of vaatwandverkalkingen. De sensitiviteit, specificiteit, en negatief voorspellende waarde van dual-source CT angiografie was hoger dan 95%. De positief voorspellende waarde was suboptimaal (<75%) en voornamelijk ten gevolge van een overschatting van lumen vernauwing bij aanwezigheid van vaatwandverkalkingen. Uit onze resultaten blijkt, dat met behulp van dual-source CT coronair angiografie zonder gebruik making van hartslag reducerende medicatie, significante vernauwingen in de kransslagvaten met een hoge sensitiviteit kunnen worden aangetoond dan wel uitgesloten.

HOOFDSTUK 3

Wij evalueerden en vergeleken de diagnostische accuraatheid van 64-slice CT coronair angiografie bij 402 symptomatische patiënten voor het detecteren van significante vernauwingen en vergeleken de uitkomsten voor mannen en vrouwen. De hoge sensitiviteit en negatief voorspellende waarde van CT coronair angiografie voor het opsporen van vernauwingen was gelijk voor mannen en vrouwen, in tegenstelling tot de specificiteit and negatief voorspellende waarde die lager was bij vrouwen. De segmentanalyse toonde bij vrouwen een lagere sensitiviteit voor het opsporen van significante vernauwingen in distale segmenten en zijtakken.

HOOFDSTUK 4

Het opsporen van significante vernauwingen in coronaire omleidingen en de daarop aangesloten distale kransslagvaten door middel van invasieve coronair angiografie in patiënten na coronair bypass chirurgie kan gecompliceerd zijn en hierdoor leiden tot een verlengde proceduretijd met langere bestralingstijd en toediening van relatief veel jodiumhoudend contrastmiddel. Wij evalueerden de potentiële meerwaarde van dual-source CT angiografie in symptomatische patiënten na coronair bypass chirurgie. De sensitiviteit voor het aantonen van een significante vernauwing in de omleidingen was 100% in de segmentanalyse, en de sensitiviteit was 95% in de aangesloten distale kransslagvaten. Wij observeerden een relatief lagere specificiteit en positief voorspellende waarde van 88% and 81%, respectievelijk, voor de natieve kransslagvaten bij patiënten met een hoge hartslag. Op basis van deze resultaten concluderen wij, dat CT

angiografie, in relatie tot het invasief coronair angiogram, eerder als complementaire dan als vervangende test moet worden beschouwd bij symptomatische patiënten na coronair bypass chirurgie. Het invasief coronair angiogram dient als primaire diagnostische test om significante vernauwingen in de natieve coronairen aan te tonen dan wel uit te sluiten.

HOOFDSTUK 5

De beoordeling van in-stent re-stenose met behulp van CT coronair angiografie kan een uitdagende opgave zijn. Metalen stents bestaan grotendeels uit structuren met een hoge dichtheid die gesuperponeerd op het lumen worden afgebeeld. Wij onderzochten de diagnostische accuraatheid van dual-source CT coronair angiografie voor het aantonen van in-stent re-stenose bij symptomatische patiënten voorafgaande aan een diagnostisch coronair angiogram. De sensitiviteit, specificiteit, positieve en negatieve predictieve waarde voor de beoordeling van alle soorten stents was respectievelijk 94%, 92%, 77% and 98%. De specificiteit was lager (64%) in stents met een diameter < 3mm. Deze resultaten toonde aan dat met behulp van CT coronair angiografie in-stent re-stenose met hoge accuraatheid kan worden aangetoond bij patiënten met terugkerende pijn op de borst na stenting. De diameter van de stent bleek van invloed te zijn op de diagnostische accuraatheid, waarbij een groter aantal vals positieve bevindingen werd waargenomen bij evaluatie van kleine stents. De negatief voorspellende waarde voor het uitsluiten van in-stent re-stenose was onafhankelijk van de stent diameter.

KLINISCHE TOEPASSING VAN CT CORONAIR ANGIOGRAFIE (DEEL 3)

HOOFDSTUK 6

De diagnostische accuraatheid van CT coronair angiografie werd vergeleken met de traditionele fietsproef bij 334 stabiele patiënten , en met single-photon emission computed tomography (SPECT) bij 61 stabiele patiënten, voor het opsporen van significante vernauwingen in de kransslagvaten. De diagnostische accuraatheid van de fietsproef was significant lager dan van CT coronair angiografie: sensitiviteit van 76% versus 100%; specificiteit van 47% versus 74%; positief voorspellende waarde van 70% versus 91%; negatief voorspellende waarde van 30% versus 99%. Er was een statistisch significant verschil in sensitiviteit tussen SPECT and CT coronair angiografie. maar niet in specificiteit. De sensitiviteit was respectievelijk 89% and 98% voor SPECT and CT coronair angiografie. De specificity was respectievelijk 77% and 82% voor SPECT and CT coronair angiografie. Wij observeerden een hoge diagnostische accuraatheid van zowel SPECT and 64-slice CT coronair angiografie, die superieur bleek aan die van de fietsproef, voor het aantonen dan wel uitsluiten van onderliggend obstructief coronair lijden bij patiënten met stabiele angina pectoris.

HOOFDSTUK 7

De toetsing van een test op basis van diagnostische accuraatheid is belangrijk, echter de klinische toepassing van een test wordt tevens bepaald door het effect van een positieve of nega-

tieve test uitslag op het daaropvolgende klinische beleid. Het is bekend, dat de diagnostische accuraatheid van een test, en dus secundair de klinische toepassing van een test, afhankelijk is van de individuele voorafkans op aanwezigheid van ziekte. Wij analyseerden de diagnostische accuraatheid van niet-invasieve inspanningsonderzoeken en CT coronair angiografie bij patiënten met een lage, intermediaire en hoge voorafkans en onderzochten de additionele waarde van de ene test ten opzichte van de andere test. Wij concludeerden dat de fietsproef een goede eerstelijns test is voor patiënten met een lage voorafkans, gezien de test relatief veilig en toegankelijk is en — in tegenstelling tot CT coronair angiografie — geen gebruik maakt van ioniserende röntgenstraling. Bij patiënten met een intermediaire voorafkans, bleek CT coronair angiografie een betrouwbare test waarbij een negatieve scan de aanwezigheid van significante vernauwingen met zekerheid uitsluit en een positieve scan voldoende zekerheid geeft om door te verwijzen naar invasieve coronair angiografie. Bij patiënten met een hoge voorafkans had CT coronair angiografie geen toegevoegde waarde en is directe verwijzing naar invasieve coronair angiografie zinvol. Het verrichten van een inspanningsonderzoek blijft echter van belang voor het aantonen dan wel uitsluiten van de aanwezigheid van cardiale ischemie met het oog op eventuele revascularisatie bij deze hoog risico patiënten.

Hoofdstuk 8

De toepassing van CT coronair angiografie vereist strikte klinische indicaties aangezien de techniek relatief duur is en patiënten bloot stelt aan ioniserende röntgenstraling en jodiumhoudend contrast middel. Uit eerder onderzoek is gebleken dat patiënten met een intermediaire voorafkans op onderliggend significant coronair lijden het meeste baat hebben bij het ondergaan van CT coronair angiografie. Wij ontwikkelden een risicoscore op basis van de klinische evaluatie, de fietsproef en de CT-kalk score voor het identificeren van patiënten met stabiele angina pectoris en een intermediaire voorafkans (20-80%) op een positief CT coronair angiogram. Wij valideerden deze risicoscore bij een onafhankelijk patiëntenpopulatie. Wij observeerden, dat het aantal patiënten met een intermediaire voorafkans op een positief CT coronair angiogram, substantieel kan worden verlaagd met 74%. Onze resultaten tonen aan dat deze risicoscore betrouwbaar is voor het identificeren van patiënten waarbij CT coronair angiografie baat heeft en dat toepassing van deze risicoscore het aantal onnodig verrichte CT coronair angiogrammen aanzienlijk kan reduceren.

Stralingsbelasting in CT coronair angiografie (deel 4)

Hoofdstuk 9

De blootstelling aan ioniserende röntgenstraling bij CT coronair angiografie kan substantieel zijn. Het gebruik van ECG - gecontroleerde stralingmodulatie ofwel 'ECG-pulsing' is een effectieve manier om de patient te beschermen tegen een overmaat aan röntgenstraling. Wij ontwikkelden een optimaal scanprotocol voor dual-source spiraal CT coronair angiografie met toepassing van ECG-pulsing in relatie tot de hartslagfrequentie. Door toepassing van ECG-pul-

sing kon de stralingsdosis aanzienlijk (tot 41%) worden verlaagd met behoud van diagnostische beeldkwaliteit, in het bijzonder bij patiënten met een lage of hoge hartfrequentie. Een verdere verlaging in stralingsdosis, van respectievelijk 38%, 9% and 41% bij patiënten met lage, intermediaire en hoge hartslagfrequenties, bleek mogelijk door verlaging van de buisstroom (4% in plaats van 20%) buiten het ECG-pulsing interval.

Hoofdstuk 10

Wij evalueerden het effect van de toepassing van standaard en optimale-ECG pulsing op de diagnostische accuraatheid van CT coronair angiografie voor het detecteren van significante kransslagvat vernauwingen, stralingsdosis en gerelateerd kanker risico bij 436 symptomatische patiënten. Het gebruik van optimale ECG-pulsing versus geen ECG-pulsing resulteerde in een verlaging van de effectieve dosis en kanker risico met 43%. Het gebruik van optimale ECG-pulsing versus standaard ECG-pulsing resulteerde in een verlaging van de effectieve dosis en kanker risico met 25%. De toepassing van optimale ECG-pulsing had geen effect op de diagnostische accuraatheid van CT coronair angiografie voor het detecteren van significante vernauwingen.

Hoofdstuk 11

Adaptieve ECG-pulsing algoritmes zijn in staat om onregelmatigheden in het hartritme te detecteren. De ECG-pulsing wordt automatisch uitgeschakeld bij bijvoorbeeld ectopische hartslagen totdat het ritme weer gestabiliseerd is. Dit adaptieve ECG-pulsing algoritme is ontwikkeld voor het behoud van diagnostische beeldkwaliteit in spiraal CT coronair angiografie bij patiënten met een onregelmatig hartritme. Wij evalueerden het effect van de hartslagfrequentie en hartslagvariabiliteit op de stralingsdosis, beeldkwaliteit en diagnostische accuraatheid van spiraal CT coronair angiografie bij toepassing van adaptieve ECG-pulsing. De stralingsdosis was significant hoger bij patiënten met een lage versus een hoge hartslagfrequentie, en in patiënten met een ernstige versus een normale hartslagvariabiliteit. De beeldkwaliteit en diagnostische accuraatheid waren onafhankelijk van de hartslagfrequentie en hartslagvariabiliteit. We observeerden een trend bij patiënten met een lage CT kalkscore waarbij een lagere specificiteit (96% vs. 91%) en positief voorspellende waarde (98% vs. 82%) waarneembaar was in patiënten met een hoge hartslagfrequentie of ernstige hartslagvariabiliteit in vergelijking met patiënten met een lage hartslagfrequentie of normale hartslagvariabiliteit.

HUIDIGE EN TOEKOMSTIGE ROL VAN CT CORONAIR ANGIOGRAFIE

Hoofdstuk 12

The rol van CT coronair angiografie binnen de diagnosestelling en beleidsbehandeling van patiënten met stabiele angina pectoris is een actueel onderwerp van klinisch onderzoek. Een voorstel voor een nieuw algoritme met CT coronair angiografie als alternatieve diagnostische test wordt gepresenteerd en tekortkomingen van CT coronair angiografie worden besproken.

Hoofdstuk 13

In dit hoofdstuk worden toekomstige onderzoekslijnen met betrekking tot CT coronair angiografie beschreven.

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4. *Detection and characterization of coronary bifurcation lesions with 64-slice computed tomography coronary angiography.*
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3. *64-Slice CT coronary angiography in patients with non-ST elevation acute coronary syndrome.*
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BOOKCHAPTERS

In: Atlas of Coronary Artery Disease With Computed Tomography. 2010 In press.

Part I - *Fundamentals in Cardiac CT: CT Fundamentals*
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Part I - *Fundamentals in Cardiac CT: Cardiac CT basics*
Maffei E, Palumbo A, Martini C, Dijkshoorn M, Capuano E, **Weustink AC,** Mollet NR, Cademartiri F

Part I - *Fundamentals in Cardiac CT: Contrast Material Administration*
Cademartiri F, Maffei E, Palumbo A, Martini, **Weustink AC,** Mollet NR

Part II - *Spectrum of Diseases: Coronary stenosis*
Meijboom WB, Neefjes-Vermunt LA, **Weustink AC,** Capuano E, Cademartiri F, Mollet NR

Part II - *Spectrum of Diseases: Coronary Artery Bypass Grafts*
Weustink AC, Capuano E, Neefjes-Vermunt LA, Palumbo A, Maffei E, Cademartiri F, Mollet NR.

Part II - *Spectrum of Diseases: Coronary Anomalies*
Weustink AC, Neefjes-Vermunt LA, Capuano E, Rengo M, Mollet NR

Part II - *Spectrum of Diseases: Coronary Calcium & Plaques*
La Grutta L, Palumbo A, Maffei E, **Weustink AC,** Pugliese F, Martini C, Mollet NR, Cademartiri F

Part II - *Spectrum of Diseases: Prognostic Value of CT Coronary Plaque Assessment*
Weustink AC, Pugliese F, Capuano E, Rossi A , Dijkshoorn ML, Mollet NR

Part III - *Clinical applications of cardiac CT & Cases: Secondary prevention*
Neefjes-Vermunt LA, **Weustink AC,** Capuano E, Rengo M, Cademartiri F, Mollet NR

Part III - *Clinical applications of cardiac CT & Cases: Acute Coronary Syndrome*
Capuano E, **Weustink AC,** Rossi A, Dijkshoorn M, Cademartiri F, Mollet NR

Part III - *Clinical applications of cardiac CT & Cases*
Rengo M, Capuano E, Neefjes-Vermunt LA, **Weustink AC,** Cademartiri F, Mollet NR

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How to perform and interpret computed tomography coronary angiography.
Mollet NR, van Pelt N, Meijboom WB, **Weustink AC,** Cademartiri F, Nieman K, Krestin GP, de Feyter PJ.

PRESENTATIONS

EUROPEAN SOCIETY OF MAGNETIC RESONANCE IN MEDICINE AND BIOLOGY, 2004

1. **Weustink AC**, van Dijke CF, Oosterhuis JW, Krestin GP. Poster presentation: Postmortem whole body CT and MRI: An alternative to conventional autopsy?

RADIOLOGICAL SOCIETY OF NORTH AMERICA, 2005

2. **Weustink AC**, Krestin GP, Oosterhuis JW, van Dijke CF. Poster presentation: Normal Post-mortem Computed Tomography and Magnetic Resonance Imaging Findings: a Guideline for Non-invasive Autopsy.

NEDERLANDSE VERENIGING VOOR RADIOLOGIE, 2006

3. **Weustink AC,** Mollet NR, Meijboom WB, de Feyter PJ, Krestin GP. Dual Source Computed Tomography Coronary Angiography.

AMERICAN HEART ASSOCIATION, 2006

4. **Weustink AC,** Mollet NR, Meijboom WB, de Feyter PJ, Krestin GP. Diagnostic Accuracy of Dual Source Computed Tomography Coronary Angiography in Patients Referred for Conventional Angiography.

5. **Weustink AC,** Mollet NR, Meijboom WB, de Feyter PJ, Krestin GP. Influence of Heart Rate on the Presence of Motion Artefacts and Image Reconstruction With Dual Source Computed Tomography Coronary Angiography.

RADIOLOGICAL SOCIETY OF NORTH AMERICA, 2006

6. **Weustink AC,** Mollet NR, Meijboom WB, de Feyter PJ, Krestin GP. Diagnostic Accuracy of Dual Source Computed Tomography Coronary Angiography in Patients Referred for Conventional Angiography.

7. **Weustink AC,** Mollet NR, Meijboom WB, de Feyter PJ, Krestin GP. Influence of Heart Rate on the Presence of Motion Artefacts and Image Reconstruction with Dual Source Computed Tomography Coronary Angiography.

8. **Weustink AC**, van Dijke CF, Wielopolski P, Hunink MG, Renken NS, Oosterhuis JW, Krestin GP. Poster presentation: Postmortem Total Body CT and Total Body MRI in a Clinical Setting; Benefits and limitations of Both Techniques.

AMERICAN COLLEGE OF CARDIOLOGY, 2006

9. **Weustink AC,** Meijboom WB, Mollet NR, de Feyter PJ, Krestin GP. Diagnostic Accuracy of Dual Source Computed Tomography Coronary Angiography in Patients Referred for Conventional Angiography.

EUROPEAN CONGRESS OF RADIOLOGY, 2007

10. **Weustink AC**, van Dijke CF, Wielopolski P, Hunink MG, Renken NS, Oosterhuis JW, Krestin GP. Postmortem whole body CT and MRI: An alternative to conventional autopsy?

RADIOLOGICAL SOCIETY OF NORTH AMERICA, 2007

11. **Weustink AC,** Nieman K, Pugliese F, Meijboom WB, van Mieghem C, Mollet N, Krestin GP, de Feyter PJ. Dual Source CT in symptomatic patients after coronary bypass surgery: evaluation of grafts and distal run-offs.

12. **Weustink AC,** van Mieghem C, Mollet N, Pugliese F, Meijboom WB, Kofflard M, Matheijssen N, den Boer A, Krestin GP, de Feyter PJ. Radiation exposure, procedure time and contrast load in patients referred for coronary angiography: Comparison of Dual Source CT with conventional coronary angiography.

13. **Weustink AC,** van Mieghem C, Meijboom WB, Pugliese F, Mollet NR, Serruys P, Krestin GP, de Feyter PJ. Clinical value of CT coronary angiography in symptomatic patients after percutaneous coronary intervention.

NEDERLANDSE VERENIGING VOOR RADIOLOGIE, 2008

14. **Weustink AC,** Mollet NR, Neefjes LA, de Feyter PJ, Krestin GP. Impact van hartfrequentie op diagnostische accuraatheid in Dual Source CT coronair angiografie.

15. **Weustink AC,** Mollet NR, Neefjes LA, de Feyter PJ, Krestin GP. Optimale ECG pulsing in Dual Source CT coronair angiografie.

RADIOLOGICAL SOCIETY OF NORTH AMERICA, 2008

16. **Weustink AC,** Mollet NR, Pugliese F, Meijboom WB, Krestin GP, De Feyter PJ. Diagnostic Accuracy of Computed Tomography Coronary Angiography in Symptomatic Patients Referred for Conventional Coronary Angiography.

17. **Weustink AC,** Mollet NR, Pugliese F, Neefjes L, De Feyter PJ, Krestin GP. Impact of Heart Rate on the Diagnostic Performance of Dual Source CT Coronary Angiography.

PHD PORTFOLIO

Name PhD student:	Annick Carine Weustink
Erasmus MC Department:	Radiology / Cardiology
Research School:	COEUR
PhD period:	September 2005- September 2008
Promotor(s):	Prof. Dr. P.J. de Feyter / Prof. Dr. G.P. Krestin

PHD TRAINING

Year	*Workload*	*Hours/ ECTS)*
General academic skills		
Biomedical English Writing and Communication	2005-2006	1.5
Research skills		
Statistics	2006	6.0
In-depth courses (e.g. Research School, Medical Training)		
COEUR (Cardiovascular Research School Erasmus MC Rotterdam)		
Pathophysiology of ischemic heart disease	2005	1.5
Atherosclerosis research	2006	1.5
Cardiovascular imaging and diagnostics	2004	.5
Peripheral vascular disease	2007	1.5
Research Seminar	2009	1.5
Virtopsy course (Bern, Zwitserland)	2007	1.5
Presentations		
Postmortem whole body CT and MRI		
European Society of Magnetic Resonance in Medicine and Biology (3 days)	2005	0.9
Radiological Society of North America (6 days)	2005	1.8
Radiological Society of North America (6 days)	2006	1.8
European Congress of Radiology (5 days)	2007	1.5
Diagnostic Accuracy of Dual Source Computed Tomography Coronary Angiography in Patients Referred for Conventional Angiography		
Nederlandse Vereniging voor Radiologie (2 days)	2006	0.6
American Heart Association (6 days)	2006	1.8
Radiological Society of North America (6 days)	2006	1.8
American College of Cardiology (6 days)	2006	1.8

Influence of Heart Rate on the Presence of Motion Artefacts and Image Reconstruction with Dual Source Computed Tomography Coronary Angiography		
Radiological Society of North America (6 days)	2006	1.8
Nederlandse Vereniging voor Radiologie (2 days)	2008	0.6
Dual Source CT in symptomatic patients after coronary bypass surgery: evaluation of grafts and distal run-offs		
Radiological Society of North America (6 days)	2007	1.8
Radiation exposure, procedure time and contrast load in patients referred for coronary angiography: Comparison of Dual Source CT with conventional coronary angiography		
Radiological Society of North America (6 days)	2007	1.8
Clinical value of CT coronary angiography in symptomatic patients after percutaneous coronary intervention		
Radiological Society of North America (6 days)	2007	1.8
Minimale invasieve obductie		
Maastricht (1 day)	2007	0.3
Diagnostic Accuracy of Computed Tomography Coronary Angiography in Symptomatic Patients Referred for Conventional Coronary Angiography		
Radiological Society of North America (6 days)	2008	1.8
Impact of Heart Rate on the Diagnostic Performance of Dual Source CT Coronary Angiography		
Nederlandse Vereniging voor Radiologie (2 days)	2008	0.6
Radiological Society of North America (6 days)	2008	1.8
CT Coronary Angiography Technical Developments & Clinical Indications		
Alkmaar	2009	0.1
Purmerend	2009	0.1
Amsterdam	2009	0.1
Deventer	2009	0.1
CT kalk score		
Groot referaat, Erasmus MC, Rotterdam & regio	2009	0.1
CONFERENCES		
European Society of Magnetic Resonance	2005	1.0
Radiological Society of North America	2005	1.0
Radiological Society of North America	2006	1.0
Nederlandse Vereniging voor Radiologie	2006	1.0

American Heart Association	2006	1.0
American College of Cardiology	2006	1.0
Europeancongress of Radiology	2007	1.0
Radiological Society of North America	2007	1.0
Nederlandse Vereniging voor Radiologie	2008	1.0
Radiological Society of North America	2008	1.0
Nederlandse Vereniging voor Radiologie	2008	1.0
European Congress of Radiology	2009	1.0
Cardiovascular and Interventional Radiological Society of Europe	2009	1.0

SEMINARS AND WORKSHOPS

Training course in cardiac CT

Cardiac CT training, Rotterdam	2006	1.0
European Congress of Radiology	2009	1.0

CURRICULUM VITAE

Annick Carine Weustink was born on November 29th 1977 in The Hague, the Netherlands. She started Medical School in 1996 at Leiden University. During her studies, she worked as a junior assistent at the department of Pathology at the Leiden University Medical Center. In 2003, she obtained her medical degree. After a half year working as a resident at the department of Pediatric Surgery at the Sophia Children's Hospital, she started her specialisation in Radiology in September 2003 at the Erasmus Medical Center in Rotterdam (supervisor Professor G.P. Krestin). She combined her first two years of training with the *Minimally Invasive Autopsy* (MIA) study under the supervision of Professor J.W. Oosterhuis (Chairman of the department of Pathology). She investigated the potential of postmortem whole-body CT and MRI in combination with ultrasound guided biopsies as an alternative to conventional autopsy. In September 2005, she temporarily paused her Radiology training to work as a research fellow under the supervision of Professor P.J. de Feyter (Department of Interventional Cardiology, Thorax Center) and Professor G.P. Krestin. Her achievements in the optimization and clinical application of CT coronary angiography are summarized in this PhD thesis. She resumed her Radiology training in September 2008.

Annick Carine Weustink is geboren op 29 november 1977 te Den Haag. In 1996 startte zij met de studie Geneeskunde aan de Universiteit Leiden. Tijdens haar studie werkte zij als studentassistent op de afdeling Pathologie van het Leids Universitair Medisch Centrum. In 2003 behaalde zij het artsexamen. Aansluitend werkte zij een half jaar als arts-assistent op de afdeling Kinderchirurgie van het Sophia Kinderziekenhuis. In september 2003 startte zij als arts-assistent in opleiding tot radioloog in het Erasmus Medisch Centrum te Rotterdam (opleider: prof. dr. G.P. Krestin). Gedurende de eerste twee opleidingsjaren combineerde zij de opleiding met het opzetten en uitvoeren van de *Minimale Invasieve Autopsy* (MIA) studie onder begeleiding van prof. dr. J.W. Oosterhuis (afdelingshoofd Pathologie). Zij onderzocht de potentie van postmortem whole-body CT en MRI in combinatie met echogeleide puncties als een alternatief voor conventionele autopsie. In september 2005 onderbrak zij tijdelijk de opleiding tot radioloog en werkte zij als arts-onderzoeker onder de begeleiding van prof. dr. P.J. de Feyter (afdeling Interventie Cardiologie, Thorax Center) en prof. dr. G.P. Krestin. Haar wetenschappelijk werk met betrekking tot optimalisatie en klinische toepassing van CT coronair angiografie is samengevat in dit proefschrift. Zij hervatte haar opleiding tot radioloog in september 2008.

ABBREVIATIONS

ACC:	accuracy
AHA:	American Heart Association
AUC:	Area under the receiver operator curve
BEIR:	Biological Effects of Ionizing Radiation
BMI:	body mass index
BMS:	bare metal stent
Bpm:	beats per minute
CA:	conventional angiography
CABG:	coronary artery bypass graft
CAD:	coronary artery disease
CCA:	conventional coronary angiography
CCS:	CT-coronary calcium score
CI:	confidence interval
cMPR:	curved multiplanar reconstruction
CT:	computed tomography
CTA:	computed tomography angiography
CTCA:	computed tomography coronary angiography
CTDI:	computed tomography dose index
CX:	circumflex coronary artery
D:	diagonal coronary branch
DES:	drug-eluting stent
DLP:	dose-length product
DS	dual-source
DSCT:	dual-source computed tomography
E:	effective dose
ECG:	electrocardiogram
ED:	end-diastole
EED:	estimated effective dose
ES:	end-systole
ICRP:	International Commission on Radiological Protection
FN:	false-negative
FP:	false-positive
HR:	heart rate
HRF:	heart rate frequency
HRV:	heart rate variability
IBD:	inter-beat difference
ICA:	invasive coronary angiography
IM:	intermediate coronary branch
LAD:	left anterior descending artery
LAR:	lifetime attributable risk
LIMA:	left internal mammary artery
LM:	left main coronary artery
LR:	likelihood ratio

MPI:	myocardial perfusion imaging
MRI:	magnetic resonance imaging
MSCT:	multi-slice computed tomography
NPV:	negative predictive value
NS:	not significant
OR:	odds ratio
PCI:	percutanous coronary intervention
PET:	positron emission tomography
PPV:	positive predictive value
PTP:	posttest probability
QCA:	quantitative coronary angiography
RCA:	right coronary artery
ROI:	region of interest
S:	septal coronary branch
SD:	standard deviation
SAS:	step-and-shoot
SPECT:	single-photon emission computed tomography
SVG:	saphenous venous graft
TN:	true-negative
TP:	true-positive
VRT:	volume rendered CT