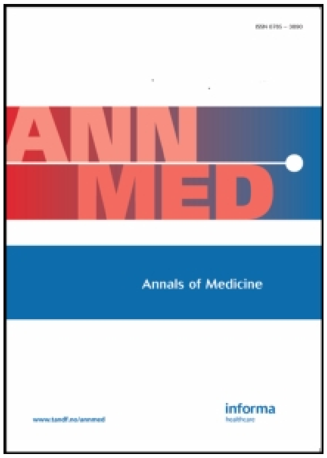

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ORIGINAL ARTICLE

Multislice cardiac computed tomography in symptomatic middle-aged women

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Abstract

Objective. To assess the accuracy of multislice cardiac computed tomography (MSCT) for detection of significant coronary artery disease (CAD) in middle-aged symptomatic women.

Methods. We included 70 women (51 ± 8 years) with complaints of chest pain or dyspnea, and an abnormal maximum exercise electrocardiogram (ECG) (8.6 ± 1.4 metabolic equivalents). All had a MSCT using a 16 detector rows scanner, and coronary arteriography (CA). Blinded results of the two modalities were compared using a segment, vessel, and patient-based analysis.

Results. On MSCT 36% had normal coronaries, 24% had significant CAD requiring revascularization, and the remainder had mild CAD. MSCT had reasonably high diagnostic accuracy at segment level (negative predictive value of 95%, positive predictive value 81%, specificity 99%, and sensitivity 50%), regarding single or multivessel CAD when both nonassessable and assessable segments were included in the analysis. The agreement between the segments comparing MSCT and CA for significant CAD was excellent at 98% (kappa value 0.89).

Conclusions. In this cohort of middle-aged symptomatic women with an abnormal stress test, 24% had significant CAD requiring intervention. MSCT was highly accurate in diagnosing significant CAD with an excellent negative predictive value.

Key words: *Coronary artery disease, multislice cardiac computed tomography, women*

Introduction

Underrepresentation of women in clinical trials and observational studies has led to a lack of available evidence and a generalized misperception that coronary artery disease (CAD) was a 'man's disease' (1–9).

The high prevalence of nonobstructive CAD and single vessel disease in women results in an observed decrease in diagnostic accuracy and higher false-positive testing in women versus men (10). Coronary artery disease in premenopausal women lags 10–15 years behind that of men until approximately the seventh decade of life (11). Although traditional risk markers for cardiovascular disease appear to underestimate risk in women (12), combined assessment of risk factors, chest pain history, and exercise tolerance may play an important role in determining the probability of CAD. Physicians may choose from a variety of noninvasive diagnostic modalities, but the accuracy and limitation of exercise testing in female patients remains an area of significant confusion. Imaging symptomatic women at intermediate to high risk of CAD has demonstrated value in guiding management decision-making and therapeutic risk reduction strategies according to the extent and severity of ischemia (13). Therefore, exercise ECG and cardiac imaging studies are recommended for those at intermediate to high pretest likelihood of CAD (13,14).

Regarding the newer noninvasive imaging modalities, multislice cardiac computed tomography

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Abbreviations

CA	coronary arteriography
CAD	coronary artery disease
MSCT	multislice computed tomography

(MSCT) offers the possibility of assessing CAD involving calcified and noncalcified plaques. The published data, however, includes only quantification of coronary artery calcium as a marker of atherosclerotic burden, and the current data indicate that CAD risk stratification is possible in women (14). Specifically, low coronary calcium scores are associated with a low adverse event risk, and high calcium scores are associated with a worse event-free survival (14,15). We sought to assess the accuracy of MSCT in ruling out significant CAD in a cohort of middle-aged symptomatic women with an abnormal exercise test.

Methods

Patients

Seventy predominantly premenopausal (58 of 70) women (age range 38–73 years, mean 51 ± 8 years) with suspected CAD were enrolled in the study. Consecutive patients assessed by a cardiologist and satisfying the following criteria were enrolled: complaints of chest pain or dyspnea usually associated with exertion, ability to perform peak (bicycle) exercise test reproducing anginal symptoms and or ischemic ECG changes (horizontal ST-segment depression of >1mm versus baseline ECG), no previous history of CAD, and sinus rhythm. The exclusion criteria were abnormal renal function (serum creatinine level >1.3 mg/dL), known allergy to iodinated contrast, and hyperthyroidism (thyrotropin level <0.25 mIU/L). In all patients the exercise ECG test was followed by a MSCT and conventional coronary arteriography (CA) within a period of 14 days. The study was approved by the local ethics committee, and informed consent was obtained from all patients.

Bicycle ergometry protocol

All patients had a bicycle ergometry, after a medical history, physical examination, and ECG were performed to rule out contraindications to testing. The cycles were calibrated in watts, and the electrically braked cycles varied the resistance to the pedaling speed, which was maintained between 60–70 rpm. Because exercise on a cycle ergometer is non-weight-bearing, watts can be converted to oxygen uptake in milliliters per minute. Metabolic equivalents (METs) were obtained by dividing VO_2 in milliliters by the product of body weight (in kg) $\times 3.5$. The number 3.5 is the accepted value assigned to oxygen uptake while at rest ($MET = 3.5$ mLO_2 kg^{-1} min^{-1}). For the test protocol, the initial power output was 30 watts, followed by increases of 15 watts per minute until end points were reached. End points were heart rate of $>85\%$ of maximum heart rate, development of ST changes (>1.0 mm horizontal or downsloping ST segment depression for 80 ms after the J point), drop in systolic blood pressure >10 mmHg (persistently below baseline) despite increase in workload, when accompanied by other evidence of ischemia, complaints of angina, dizziness or near syncope, sustained ventricular tachycardia, and patient's request to stop. The postexercise monitoring was continued for at least 8 minutes, or until blood pressure, heart rate, and ST segments approximated to baseline values. The tests were supervised by experienced physicians appropriately trained to administer exercise tests. The subjective rating of the intensity of exertion perceived by the exercising person was also noted, as this is a sound indicator of relative fatigue.

Key messages

- In 70 symptomatic middle-aged women without prior known coronary artery disease, and with an abnormal maximum exercise ECG test, 24% had significant coronary artery disease requiring revascularization, all of whom were accurately diagnosed by multislice cardiac computed tomography (MSCT), with a negative predictive value of 95%–100%.
- The total MSCT plaque burden provides additional information about the extent, distribution and location of coronary atherosclerosis, may potentially render coronary arteriography unnecessary, and also have important implications in view of preventive measures and risk factor modifications.

CT imaging protocol

The ECG was recorded during the entire scanning protocol. At heart rates above 70 bpm intravenous metoprolol was administered up to a maximum dose of 10 mg unless contraindicated (chronic obstructive pulmonary disease), and some patients received an additional single dose of sublingual 1 mg lorazepam. All patients were examined on a 16-row MSCT scanner (Sensation 16, Siemens, Forchheim, Germany). Scan parameters were as follows: 16×0.75 mm collimation, rotation time 420 ms; table feed 3.0 mm/rotation; tube voltage 120 kV; effective dose in mAs 500–600 (depending on age and weight/length). There was no prospective X-ray tube modulation. Studies were preceded by a scout acquisition. The estimated radiation exposure using this scan protocol is 11.8–16.3 mSv (Male–Female; WinDose, Institute of Medical Physics, Erlangen, Germany).

For the CT angiography, a bolus of 90 mL contrast material (mean flow rate 5 mL/sec) with iodine content 400 mg/mL (Iomeron 400, Bracco, Milan, Italy) was injected through an arm vein followed by a 50-mL saline flush. A bolus tracking technique was used to synchronize the arrival of the contrast in the coronary arteries with the initiation of the scan. To monitor the arrival of contrast material, axial scans were obtained at the level of the ascending aorta with a delay of 10 seconds after the start of the contrast injection. The scan was automatically started when a threshold of 100 Hounsfield units was reached in a region of interest positioned in the ascending aorta. Data were acquired during a breath-hold of 19 ± 2 seconds. Images were reconstructed with ECG gating to obtain optimal, motion-free image quality, from standard data sets reconstructed during mid-to-end diastole (350, 400, 450 ms before the next R-wave). In case of suboptimal image quality, additional reconstructions were obtained at the end-systolic phase (between 25% and 35% of the R-R interval). If necessary, multiple data sets of a single patient were used separately to obtain optimal image quality of all available coronary segments.

All MSCTs were analyzed using an offline workstation (Leonardo, Siemens) by two experienced readers. A 12-segment model was used (left main, proximal-, mid- and distal left anterior descendens and right coronary artery, proximal and distal circumflex, first marginal branch, posterior descendens, and first diagonal or intermediate branch), and all segments regardless of size were included for comparison with coronary arteriography. On MSCT, maximum intensity projections, curved multiplanar reconstructions and cross-sectional multiplanar reformatted images were used to classify segments as normal (smooth, without any calcified or noncalcified plaque), nonsignificant stenosis (mild to moderate or $<50\%$ reduction in luminal diameter), intermediate stenosis (50%–70% reduction in luminal diameter), or significant stenosis ($>70\%$). Image quality was evaluated on a per-segment basis and classified as adequate or inadequate due to image degrading artifacts related to motion, calcification or low vessel lumen opacification.

Coronary arteriography protocol

The coronary arteriography was performed within 14 days of the MSCT, using a 6F Judkins diagnostic catheter, and injection of standard nonionic contrast media. Lesions in each of the epicardial coronary arteries were assessed by an experienced interventional cardiologist, unaware of the MSCT results. The segments were classified as normal, nonsignificant stenosis, intermediate stenosis (50%–70%) or significant stenosis ($>70\%$) requiring revascularization. In case of an intermediate stenosis, a pressure wire was employed to assess the hemodynamic significance of the stenosis. A fractionated flow reserve measurement of <0.75 was considered as significant stenosis. A stenosis of $>70\%$ was considered suitable for revascularization considering the symptomatic status of the patient in combination with an abnormal exercise test.

Statistics

Comparison between MSCT and CA was done at a segment level, vessel level (no or any disease per vessel), and patient level. For vessel-based analysis the segments of one vessel branch were combined. Vessels with one or more significantly obstructed segments were encoded as stenotic for comparison with CA. The patient-based analysis was performed in two ways: including all patients regardless of segment or vessel exclusions, and excluding patients with one or more segments with low image quality. Further data analysis included assessable as well as nonassessable segments and vessels (vessels with single segment exclusions were marked as excluded for vessel-based analysis). The nonassessable data was considered to be false-negative. The diagnostic performance of MSCT for detection of significant coronary stenosis (requiring revascularization) using conventional angiography as the standard of reference is presented as sensitivity, specificity, positive and negative predictive values with the corresponding 95% confidence intervals. Concordance between MSCT and CA, and inter- and intraobserver variability for significant stenosis was tested with kappa statistics. All statistical calculations were performed using Statview 5+.

Table I. Patient characteristics. Values presented as mean ± SD. Values in parentheses are percentages.

	$n=70$
Age (years)	51 ± 8
Body mass index (kg/m^2)	26.1 ± 3.2
Systolic/diastolic BP (mmHg)	134 ± 23/79 ± 11
Smoking	7/70 (10%)
Arterial hypertension	23/70 (32.9%)
Diabetes mellitus	5/70 (7.1%)
COPD/asthma	3/70 (4.3%)
Family history of cardiac disease	5/70 (7.1%)
Total cholesterol (mg/dL)	221 ± 40
HDL-cholesterol (mg/dL)	62 ± 18
LDL-cholesterol (mg/dL)	130 ± 37
Triglycerides (mg/dL)	124 ± 52
Framingham risk score	5.4 ± 5.1
Complaints of chest pain	50/70 (71.4%)
Complaints of dyspnea	43/70 (61.4%)
Bicycle ergometry (METs)	8.6 ± 1.4

COPD = chronic obstructive pulmonary disease; MET = metabolic equivalent (3.5 $mLO_2\ kg^{-1}\ min^{-1}$).

Results

Patient characteristics are shown in Table I, with about one-third of the patients being treated for hypertension. The exercise test was performed maximally in 65 patients (93%) at 8.6 ± 1.4 METs with the heart rate at > 85% of maximum heart rate, and patients developed anginal symptoms at peak exercise or during recovery with or without ST changes on the ECG. The level of perceived exertion was very hard for the patients corresponding with a Borg scale of > 18, which indicates that the subject performed maximal exercise, exceeding the anaerobic threshold. In five patients the test was stopped earlier (6.9 ± 0.8 METs) due to highly significant ST changes and symptoms. During the MSCT scan the resting heart rate was 72.5 ± 10.1 bpm, and 71% of the patients (50 of 70) received intravenous metoprolol. The mean heart rate dropped to 59.6 ± 7.7 bpm. Ninety five percent of the segments (796 of 840) were assessable, with mid and distal right coronary artery and distal circumflex mainly comprising the nonassessable segments. On CA, which was considered as the reference standard, 10 of the 70 patients had a ramus intermedius, making a total of 220 major coronary arteries to be assessed.

Segment-based evaluation

There was no patient with significant left main disease. For the segment-based evaluation, analysis of assessable segments (796 of 840) was done for agreement between MSCT and CA for significant CAD (see Table II). From the 54 segments with significant CAD on MSCT, 44 were confirmed on CA, with 1 proximal segment of the left anterior descending coronary artery, 3 mid segments of the right coronary artery, 2 distal segments of the circumflex coronary artery, and 4 distal segments of the right coronary artery being false-positive on MSCT. Of the remaining 10 false-positive segments, Fractional Flow Reserve (FFR) was determined on 2 segments, being respectively 0.88 and 0.85. There were no false-negatives, giving a sensitivity of 100%, specificity of 99%, negative predictive value of 100%, and positive predictive value of 82%. In a second analysis all segments were included ($n=44$ nonassessable were considered false-negative) (see Table III). With this the sensitivity dropped, but the specificity remained high at 99%, with a negative predictive value of 98%, and positive predictive value of 81%. Actually only 5 of the 44 nonassessable segments on MSCT had significant obstruction on CA (1 distal circumflex, 2 mid and 2 distal segments of the right coronary artery). Also these segments were prospectively judged not assessable and excluded from the first analysis, thereby not influencing the accuracy of MSCT significantly. The agreement between the segments comparing MSCT and CA for significant CAD was excellent at 98% (kappa value 0.89). The inter- and intraobserver concordance was very good at a kappa value of respectively 0.76 and 0.82 for all assessable segments.

Table II. Diagnostic accuracy of 16-slice CT coronary angiography for the detection of significant stenoses as confirmed by conventional angiography. The data presents assessable segments. Values in parentheses are percentages or 95% confidence intervals.

	Segments	Vessels	Patients
Stenosis on MSCT	54/796 (6.8%)	35/220 (15.9%)	21/70 (30%)
False-positive (MSCT)	10	3	4
False-negative (MSCT)	0	0	0
Sensitivity (MSCT)	100 (92%–100%)	100 (89%–100%)	100 (82%–100%)
Specificity (MSCT)	99 (97%–99%)	98 (95%–99%)	93 (83%–97%)
Positive predictive value (MSCT)	82 (69%–90%)	91 (78%–97%)	81 (60%–83%)
Negative predictive value (MSCT)	100 (99%–100%)	100 (98%–100%)	100 (93%–100%)

Table III. Diagnostic accuracy of 16-slice CT coronary angiography for the detection of significant stenoses as confirmed by conventional angiography. The data presented below included assessable as well as nonassessable segments. Values in parentheses are percentages or 95% confidence intervals.

	Segments	Vessels	Patients
Stenosis on MSCT	54/840 (6.4%)	38/220 (17.3%)	23/70 (32.9%)
False-positive (MSCT)	10	6	6
False-negative (MSCT)	44	3	2
Sensitivity (MSCT)	50 (40%–60%)	91 (78%–97%)	89 (69%–97%)
Specificity (MSCT)	99 (97%–99%)	97 (93%–99%)	90 (80%–95%)
Positive predictive value (MSCT)	81 (72%–87%)	84 (74%–97%)	74 (54%–87%)
Negative predictive value (MSCT)	95 (93%–96%)	98 (95%–99%)	96 (88%–99%)

Patient- and vessel-based evaluation

There were 6 patients with significant single vessel and 11 with significant multivessel CAD on CA (24% of 70 patients), all of whom were correctly identified by MSCT. There were 6 false-positive patients on MSCT, of whom 2 had one or more segments with low image quality. Exclusion of these from the analysis improved the accuracy of MSCT. However, when these were included as false-negatives in the analysis, sensitivity of 89% and specificity of 90% was obtained, with negative and positive predictive values of, respectively, 96% and 74%. At the vessel-based analysis, significant stenosis was confirmed in 32 of the 38 vessels considered to have significant stenosis on MSCT. Also when the three vessels considered to have at least one segment with low image quality were considered as false-negatives, the accuracy of MSCT remained high (see Tables II and III).

Discussion

This is the first study assessing the diagnostic accuracy of a new noninvasive cardiac imaging modality, MSCT, in detecting significant CAD in middle-aged symptomatic women with an abnormal stress test. Thirty six percent had normal coronaries, and 24% (17 of 70 patients) of these women had significant CAD requiring revascularization. High diagnostic accuracy was achieved with MSCT at segment, vessel, and patient level for significant CAD.

Because of its simplicity, lower cost, and widespread familiarity in its performance and interpretation, the standard treadmill ECG is the most reliable exercise test to select in patients with a normal resting ECG who are able to exercise. The accuracy of exercise ECG in women, however, is highly variable and influenced by multiple factors, including exercise capacity and hormonal status.

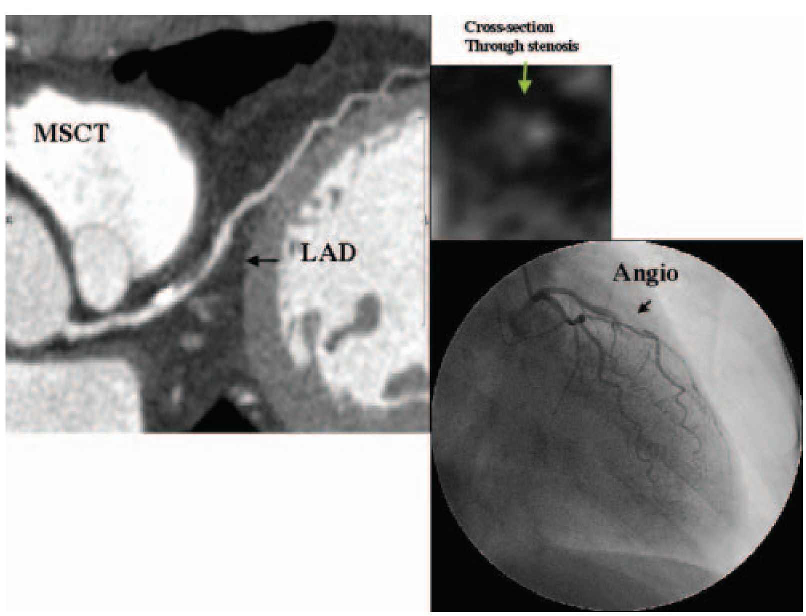

Figure 1. A 54-year-old woman with complaints of exertional fatigue performed a good exercise test (10 METs), and developed chest pain in the recovery period, without significant ECG changes. Significant mid-LAD stenosis (arrow) was found on multislice cardiac computed tomography (MSCT) caused by a noncalcified plaque, which is confirmed (arrow) on coronary arteriography (angio).

Figure 2. 3-D (volume rendering) image showing remodeling of the coronary artery and the large mid-LAD plaque (black arrow) found in the patient depicted in Figure 1.

Numerous reports have demonstrated the low diagnostic accuracy for exercise electrocardiography in women, in particular the occurrence of 1 mm of ST-segment depression or greater (16–18). For the premenopausal woman, endogenous estrogen has a digoxin-like effect that may precipitate ST-segment depression, resulting in a false-positive test result (19). Physicians who test premenopausal women with chest pain or established CAD should caution against the use of exercise stress testing in a woman's mid-cycle, during which the estrogen levels are the highest (20).

Based on the Duke treadmill score risk categories (21), generally the high-risk category should be referred to CA, and the low to moderate risk category referred for additional risk stratification with a cardiac imaging study.

In our cohort of middle-aged symptomatic women with an abnormal stress test, almost 36% had normal coronaries, and the remainder had CAD ranging from mild to moderate to significant, of whom 17 of 70 (24%) were revascularized. Gated myocardial perfusion single-photon emission computed tomography (SPECT) and dobutamine stress echocardiography have consistently better sensitivities and specificities in women with multivessel coronary disease (22–25). However, these diagnostic techniques have their limitations concerning single vessel disease, and nonsignificant obstructive CAD. The diagnostic accuracy of SPECT in women, for example, is adversely affected by gender-specific factors, such as breast attenuation, small left ventricular chamber size, and a high prevalence of single vessel CAD (26,27). Our study shows diagnostic accuracy values comparable to a large cohort of patients which included primarily men (69%) referred for conventional angiography (28), and other 16-slice MSCT studies (29,30). The more

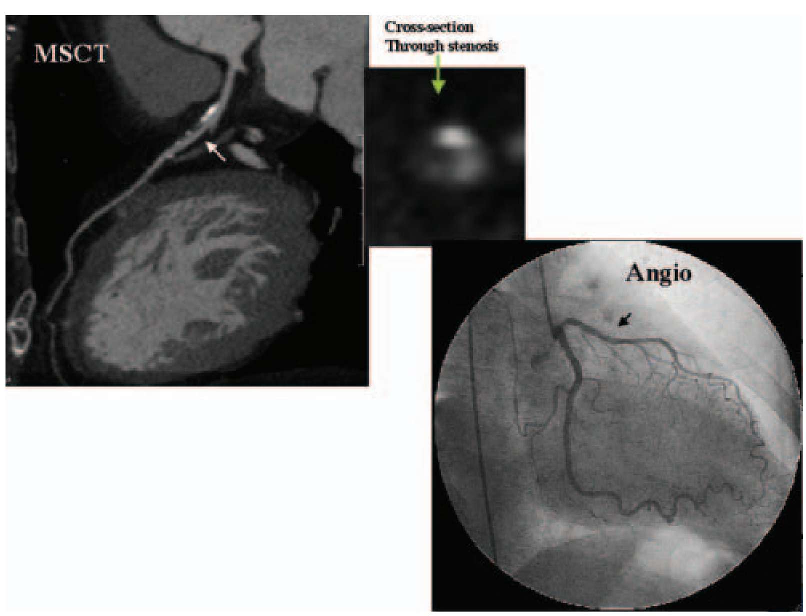

Figure 3. A 56-year-old woman with complaints of exertional angina, performed a good exercise test (8 METs), and became short of breath at peak exercise accompanied by significant ECG changes. The proximal-LAD (arrow) showed remodeling and a 50%–70% stenosis on multislice cardiac computed tomography (MSCT) caused by a mixed plaque, which was considered to be a mild stenosis on coronary arteriography (angio).

recent studies using the 64-slice technology report sensitivities and specificities between 91% and 100% (31–33). All these studies, however, took only assessable segments into consideration.

In our study, MSCT accurately diagnosed significant CAD requiring revascularization, but was also able to assess mild to moderate CAD in middle-aged symptomatic women. These findings may potentially render CA unnecessary in this particular cohort of patients, but have important implications in view of preventive measures and risk factor modifications. The total MSCT plaque burden provides additional information about the extent, distribution, and location of coronary atherosclerosis and might correlate more closely with the total plaque burden found on histology (34).

Limitations of the study

There are a number of limitations to the study and the techniques used. Irregular cardiac rhythm is an important limitation of MSCT. The use of iodinated contrast media is a limitation in certain patient populations (diabetics, patients with renal dysfunction). The radiation dose for MSCT using the technology in the present study is 11.8–16.3 mSv, which is not negligible compared to CA (7–10 mSv), and SPECT sestamibi (12–16 mSv, rest-stress imaging). We did not use ECG modulation in our study, as the patients received standard tests offered at our institution. ECG modulation allows for substantial radiation dose savings (up to 50%) without image quality impairment for regular heart rates below 65 bpm. This may be of interest especially in this subgroup of premenopausal women. The newer generation CT scanners promise to allow radiation dose reduction with ECG-modulation and by use of special cardiac image filters. Beta-blockade was used in our study to optimize the heart rate. This is, however, the standard practice at our institution. Fast developing technology, with the newer generation scans may render use of beta-blockers unnecessary. The high number of nonassessable segments is a significant limitation, and inclusion of only assessable segments may increase accuracy of the technique; however, these segments were prospectively judged as not assessable in most published studies. In our study even if the nonassessable segments (44 of 840, or 5%) were considered to be false-negative, the sensitivity dropped, but specificity and negative predictive value remained high (99%, respectively 95%), with a positive predictive value of 81%. For a new modality to have clinical utility, a very good negative or positive predictive value is required. In any case only 5 of 44 segments not assessable on MSCT showed significant obstruction on CA. It is possible that the sensitivity will increase with increasing likelihood of multivessel CAD.

Finally, MSCT is an exciting tool with tremendous diagnostic potential. The strength of MSCT lies in the direct visualization of the coronaries, uninfluenced by hormonal status, and the technique may be superior to coronary calcium determination alone, due to direct imaging of the coronaries inclusive of noncalcified plaques. Our study is potentially important given that little data currently exists with respect to application of MSCT in symptomatic women. Further studies are required to determine whether our findings can be extrapolated to various cohorts of women.

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