

Noninvasive Angiography and Assessment of Left Ventricular Function Using Multislice Computed Tomography in Patients With Type 2 Diabetes

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OBJECTIVE — Early identification of coronary artery disease (CAD) in patients with diabetes is important because these patients are at increased risk for CAD and have worse outcome than nondiabetic patients after CAD is diagnosed. Recently, noninvasive coronary angiography and assessment of left ventricular function has been demonstrated with multislice computed tomography (MSCT). The purpose of the present study was to validate this approach in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — MSCT was performed in 30 patients with confirmed type 2 diabetes. From the MSCT images, coronary artery stenoses ($\geq 50\%$ luminal narrowing) and left ventricular function (left ventricular ejection fraction, regional wall motion) were evaluated and compared with results of conventional angiography and two-dimensional echocardiography.

RESULTS — Two hundred twenty of 256 coronary artery segments (86%) were interpretable with MSCT. In these segments, sensitivity and specificity for detection of coronary artery stenoses were 95%. Including the uninterpretable segments, sensitivity and specificity were 81 and 82%, respectively. Bland-Altman analysis in the comparison of left ventricular ejection fractions demonstrated a mean difference of $-0.48 \pm 3.8\%$ for MSCT and echocardiography, which was not significantly different from 0. Agreement between the two modalities for assessment of regional contractile function was excellent (91%, κ statistic 0.81).

CONCLUSIONS — Accurate noninvasive evaluation of both the coronary arteries and left ventricular function with MSCT is feasible in patients with type 2 diabetes. This noninvasive approach may allow optimal identification of high-risk patients.

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Type 2 diabetes is a major risk factor for coronary artery disease (CAD) and is associated with a two- to four-fold increase in the risk of CAD (1). Furthermore, prognosis of patients with type 2 diabetes and confirmed CAD has been

demonstrated to be worse than in nondiabetic patients with CAD. For example, the likelihood of developing myocardial infarction is significantly higher in diabetic patients with unstable angina than in nondiabetic individuals. Moreover,

mortality rate after myocardial infarction has also been shown to be doubled (2). Early identification of CAD is, therefore, of paramount importance in patients with diabetes.

Noninvasive testing including myocardial perfusion scintigraphy and dobutamine stress echocardiography have been used to detect CAD (3,4). However, direct visualization of the coronary arteries may be preferred because patients with diabetes frequently have diffuse, multivessel CAD. Currently, conventional angiography is performed to evaluate the presence and extent of CAD. However, this is an invasive approach associated with a minimal but definitive risk of complications, and a noninvasive technique that is capable of direct visualization of the coronary arteries would be preferred. A promising new imaging technique for the noninvasive detection of CAD is multislice computed tomography (MSCT), which allows the acquisition of high-quality images of the entire heart within a single breath-hold. Several studies have demonstrated the technique to be useful in the detection of coronary artery stenoses with sensitivities and specificities ranging from 72 to 95% and 75 to 99%, respectively (5–11).

In addition, MSCT allows simultaneous assessment of left ventricular function, which is also an important prognostic parameter (4). Although the studies on assessment of left ventricular function with MSCT are scarce, the initial results demonstrated a good relation between left ventricular ejection fraction assessed by MSCT and two-dimensional echocardiography or magnetic resonance imaging (MRI) (12–14).

Combined assessment of left ventricular function and the coronary artery status with MSCT may allow optimal noninvasive evaluation of patients with diabetes and suspected CAD. To date, the value of MSCT has not been evaluated in patients with diabetes. Accordingly, the purpose of the present study was to per-

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Abbreviations: CAD, coronary artery disease; MRI, magnetic resonance imaging; MSCT, multislice computed tomography.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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form a combined assessment of coronary arteries and left ventricular function in patients with type 2 diabetes using MSCT; the results were compared with conventional angiography and two-dimensional echocardiography, respectively.

RESEARCH DESIGN AND METHODS

The study group consisted of 30 patients with known type 2 diabetes who were scheduled to undergo conventional angiography because of symptoms of angina. Criteria for the diagnosis of diabetes, as recommended by the American Diabetes Association (15), were 1) symptoms of diabetes plus casual plasma glucose concentration ≥ 200 mg/dl (11.1 mmol/l) or 2) fasting plasma glucose level ≥ 126 mg/dl (7.0 mmol/l). Exclusion criteria were atrial fibrillation, renal insufficiency (serum creatinine > 120 mmol/l), known allergy to iodine contrast media, severe claustrophobia, and pregnancy.

The average interval between conventional angiography and MSCT was 17 ± 27 days, whereas two-dimensional echocardiography was performed before or after the computed tomography examination within 2 weeks. All patients gave written informed consent to the study protocol, which was approved by the local ethics committee.

MSCT data acquisition

In the initial 12 patients, MSCT was performed using a Toshiba Multi-Slice Aquilion 0.5 (collimation 4×2.0 mm) system and in the remaining 18 patients using a Toshiba Multi-Slice Aquilion 16 system (collimation 16×0.5 mm) (Toshiba Medical Systems, Otawara, Japan). Rotation time was 0.4 or 0.5 s, depending on the heart rate, while the tube current was 250 mA at 120 kV. A bolus of 140 ml contrast (Xenetix 300, Guerbet, Aulnay S. Bois, France) was administered with an injection rate of 4 ml/s in the antecubital vein. To time the scan, automated peak enhancement detection in the aortic root was used. The heart was imaged from the aortic root to the cardiac apex during inspiratory breath-hold; electrocardiography was performed simultaneously for retrospective gating of the data. To assess left ventricular function, 20 cardiac phases were reconstructed in the short-axis orientation, with a slice thickness of 2.00 mm, and subsequently transferred to a remote workstation with dedicated car-

diac software (MR Analytical Software System [MASS], Medis, Leiden, the Netherlands).

To evaluate the coronary arteries, five reconstructions covering diastole (65–85% of the R-R range) were generated with a slice thickness of either 1.0 mm (4-slice system) or 0.5 mm (16-slice system). If motion artifacts were present, additional reconstructions were made at 40, 45, and 50% of the cardiac cycle. Images were transferred to a remote workstation (Vitrea2, Vital Images, Plymouth, MN) for postprocessing.

MSCT data analysis

Stenosis assessment was performed using a modified American Heart Association/American College of Cardiology segmentation model: the left main coronary artery (segment 5), the right coronary artery (segments 1–3 and, if present, 4 and 16), the left anterior descending coronary artery (segments 6–9), and the left circumflex artery (segment 11, 13, and if present 12, 14, 15, and 17). Only side branches of ≥ 1.5 mm, as determined by quantitative coronary angiography, or supplied by coronary bypass grafts were evaluated. Images were evaluated by an experienced observer blinded to the catheterization results, using both the original axial MSCT images and curved multiplanar reconstructions. Each segment was first evaluated as interpretable or not. Subsequently, the presence of significant narrowing ($\geq 50\%$ reduction of lumen diameter) was determined in the assessable segments. In addition, coronary bypass grafts, if present, were evaluated for the presence of $\geq 50\%$ luminal narrowing or not. In those patients, native coronary segments before the anastomosis of a patent graft were not evaluated.

Regional wall motion was assessed visually using the short-axis slices (displayed in cine-loop format) by one observer blinded to all other data using a previously described 17-segment model (16). Each segment was assigned a wall motion score using a four-point scale (1 = normokinesia, 2 = hypokinesia, 3 = akinesia, and 4 = dyskinesia). Left ventricular ejection fraction was calculated using semiautomated endocardial contour detection with manual correction when necessary. Papillary muscles were regarded as being part of the left ventricular cavity.

Table 1—Clinical characteristics of the study population

Sex (men/women)	26/4
Age (years)	62 ± 10
β -Blocking medication	16 (53)
Heart rate during acquisition	69 ± 13
Type 2 diabetes	30 (100)
Average HbA _{1c} (%)	6.9 ± 1.4
Other risk factors for CAD	
Hypertension	16 (73)
Smoking	12 (56)
Hypercholesterolemia	21 (95)
Family members with CAD	12 (56)
History	
Previous myocardial infarction	20 (67)
Previous PCI/CABG	21 (70)/11 (37)
Vessel disease	
One vessel	6 (20)
Two vessel	6 (20)
Three vessel	16 (53)
Angina pectoris	
CCS class 1 or 2	7 (23)
CCS class 3 or 4	23 (77)
Heart failure	
NYHA class 1 or 2	25 (83)
NYHA class 3 or 4	5 (17)

Data are means \pm SD or *n* (%). CABG, coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

Conventional angiography

Conventional angiography was performed according to standard techniques. Vascular access was obtained using the femoral approach with the Seldinger technique. Coronary angiograms were visually evaluated by an experienced observer blinded to the MSCT data.

Two-dimensional echocardiography

Patients were imaged in the left lateral decubitus position using a commercially available system (Vingmed System FiVe/Vivid-7, GE-Vingmed, Milwaukee, WI). Images were acquired using a 3.5-MHz transducer at a depth of 16 cm in the parasternal and apical views. Regional wall motion was analyzed using the same 17-segment model and four-point scale as described above. Left ventricular ejection fractions were calculated from the two- and four-chamber images using the biplane Simpson's rule (17).

Statistical analysis

Sensitivity, specificity, positive predictive values, and negative predictive values for

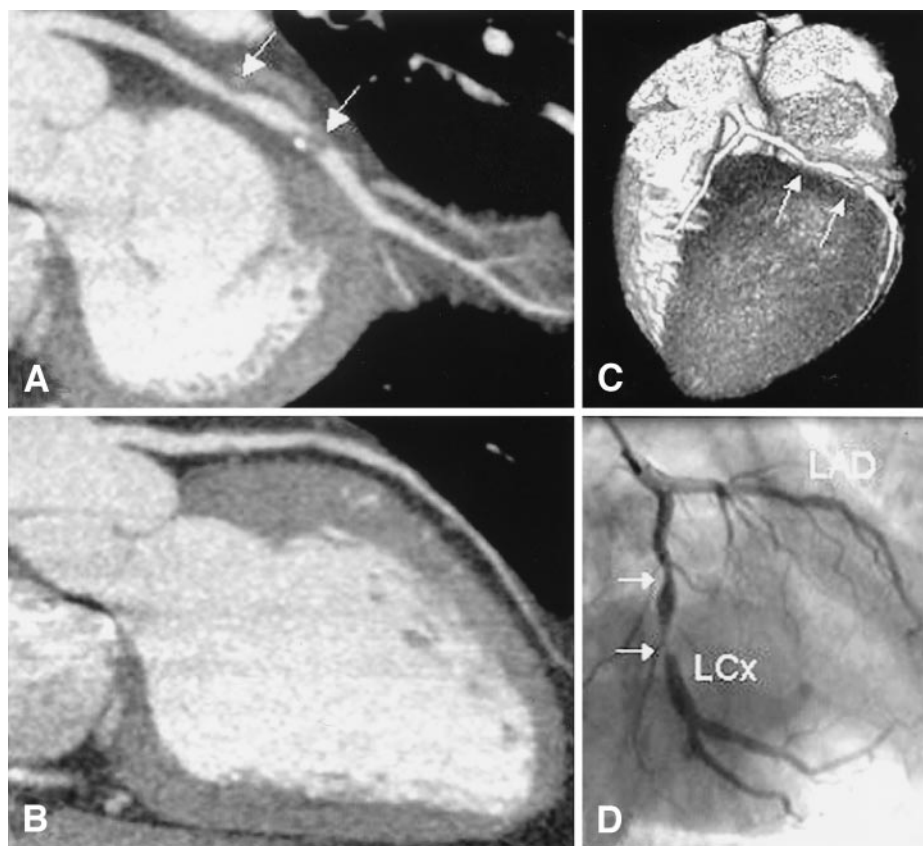


Figure 1—Curved multiplanar reconstruction of a left circumflex coronary artery (LCx) with severe narrowing of the lumen (A). No abnormalities, however, were observed in the left anterior descending coronary artery (LAD) of this patient (B). Also, in the three-dimensional volume-rendered reconstruction (C), stenoses in the LCx as well as patency of the LAD are clearly visible. Findings were confirmed by conventional X-ray angiography (D).

the detection of significant coronary artery stenoses were calculated. In addition, a patient-based analysis was performed. MSCT was considered correct in the individual patient analysis if at least one significant stenosis was detected on the MSCT images or if MSCT ruled out the presence of any significant stenosis. Pretest likelihood of CAD in patients without previous myocardial infarction or coronary bypass grafting was estimated using the Diamond-Forrester method (18). Bland-Altman analysis was performed for each pair of values of left ventricular ejection fraction to calculate limits of agreement and systematic error between the two modalities (19). Agreement for regional wall motion was expressed in a 4×4 table using weighted κ statistics. A κ value of <0.4 represents poor agreement, a κ value between 0.4 and 0.75 fair to good agreement, and a κ value of >0.75 an excellent agreement, based on the Fleiss' classification (20). A P value <0.05 was considered to indicate statistical significance.

RESULTS— The patient characteristics are summarized in Table 1. The study group consisted of 30 patients with type 2

diabetes (26 men; mean age 62 ± 10 years). The average duration of diabetes was 2.9 ± 4.4 years at the time of MSCT. A total of 11 patients received oral hypoglycemic medication or insulin ($n = 5$). Cardiac medication was continued during the study period. A total of 16 (53%) patients used β -blocking agents, and no additional β -blocking agents were administered in preparation for the scan.

Coronary artery stenoses

A total of 256 coronary segments were present for evaluation by both MSCT and conventional angiography. Of the 99 segments studied with four-slice MSCT, 18 (18%) were uninterpretable, whereas 18 of 157 (11%) segments acquired with 16-slice MSCT also were of nondiagnostic quality. Therefore, 36 (14%) segments were classified as uninterpretable. In the remaining 220 segments, conventional angiography revealed 59 significant ($\geq 50\%$ diameter reduction) lesions. Evaluation of the MSCT images resulted in the correct identification of 56 (95%) stenoses. In 153 of 161 (95%) segments, the presence of significant stenosis was correctly ruled out. Therefore, resulting sen-

sitivity and specificity were 95%. When the uninterpretable segments were included in the analysis, resulting sensitivity and specificity were 81 and 82%, respectively.

A total of 21 grafts were present (5 arterial, 16 venous). Conventional angiography revealed the presence of $\geq 50\%$ luminal narrowing in nine grafts. MSCT correctly identified all nine grafts with significant stenosis, whereas 9 of 12 grafts without significant stenosis were correctly identified on the MSCT images. In the three remaining grafts, however, the presence of significant narrowing could not be evaluated, although patency of the graft could be assessed correctly.

On a per patient basis, MSCT was accurate in 26 of 30 patients (87%). In seven patients, no significant abnormalities were observed during conventional angiography, and five (71%) of these patients were correctly identified as having no significant lesions using the MSCT images. Of the remaining 23 patients with significant lesions on conventional angiography, 21 (91%) were correctly identified using MSCT.

In 23 patients, presence of CAD was

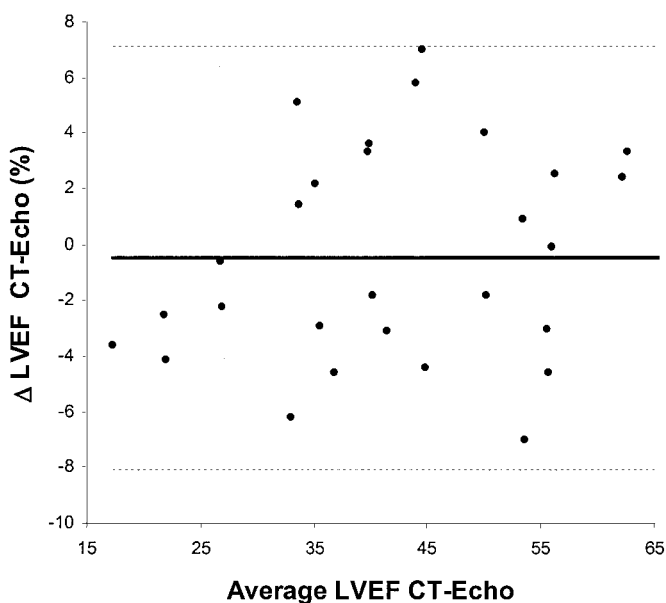


Figure 2—Bland-Altman plot in the comparison of MSCT and echocardiography in the assessment of left ventricular ejection fraction (LVEF). The difference between each pair is plotted against the average value of the same pair (solid line, mean value of differences; dotted lines, mean value of differences ± 2 SD).

known. In the remaining seven patients with suspected CAD, the pretest likelihood according to Diamond-Forrester was intermediate in two patients and high in five patients. Conventional angiography demonstrated the presence of significant lesions in five patients, of which four (80%) were correctly identified with MSCT. Of the two patients without significant CAD, one (50%) was correctly assessed with MSCT. Examples of MSCT images of both a stenotic and nonstenotic coronary artery with the corresponding angiographic images are shown in Fig. 1.

Left ventricular function

From one patient, MSCT data were lost (due to technical errors) after successful acquisition; therefore, data from 29 patients were available for left ventricular function analysis.

Mean left ventricular ejection fraction, as determined by echocardiography and MSCT, was $43 \pm 14\%$ (range 19–75%) and $43 \pm 14\%$ (15–72%, ns), respectively. Bland-Altman analysis in the comparison of computed tomography and echo left ventricular ejection fraction demonstrated a mean difference of $-0.48 \pm 3.8\%$, which was not significantly different from 0 (Fig. 2).

Echocardiography revealed contractile dysfunction in 157 of 493 segments

(32%); 71 (45%) showed hypokinesia, 74 (47%) showed akinesia, and 12 (8%) showed dyskinesia. In 149 of the dysfunctional segments (95%), decreased systolic wall thickening was also observed on the MSCT images. An excellent agreement was shown between the two techniques; 91% of segments were scored identically on both modalities (κ statistic 0.81 ± 0.03). Agreements for the individual gradings (1–4) were 97, 82, 73, and 92%, respectively. In Fig. 3, examples of short-axis reconstructions are shown, illustrating patients with and without wall motion abnormalities.

CONCLUSIONS— Our study demonstrates that noninvasive coronary angiography is feasible in patients with diabetes. An excellent sensitivity and specificity of both 95% were shown for the detection of coronary artery stenoses. Corresponding positive and negative predictive values were 88 and 98%, respectively. With inclusion of the uninterpretable segments, sensitivity and specificity were still 81 and 82%, respectively. Moreover, although inclusion of uninterpretable segments resulted in a positive predictive value of 62%, the negative predictive value remained high (92%), which is in line with previous studies (11,21). This is an important find-

ing, because clinical management is often difficult in patients presenting with diabetes and suspected CAD. In a substantial number of patients, noninvasive tests are inconclusive and knowledge of coronary anatomy (by means of invasive angiography) is often needed to determine the most optimal treatment strategy. The high accuracy of MSCT in the exclusion of CAD as demonstrated by the high specificity and negative predictive value in the current study underscores the potential of this technique to function as a first-line diagnostic modality in the workup of patients with suspected CAD. By ruling out the presence of significant stenoses, risks and costs of invasive angiography can thus be avoided in a substantial number of patients. Moreover, accurate information of coronary anatomy and extent of atherosclerosis as well as cardiac function is obtained, which may optimize treatment strategy and prognostification and may eventually even serve as a guide for interventional procedures. However, further prognostic studies are needed in larger cohorts before MSCT can become an established diagnostic tool and replace conventional coronary angiography in certain patient groups.

In addition, left ventricular function analysis was performed after retrospective reconstruction of the acquired data. In the assessment of left ventricular ejection fraction, a close correlation was observed between MSCT and two-dimensional echocardiography. Mean left ventricular ejection fraction as determined by MSCT was slightly less than the echocardiographic results, but no statistical difference was reached. A slight underestimation of left ventricular ejection fraction with MSCT has been reported previously (12–14), which may be attributed to an overestimation of LV end-systolic volume. Because minimal ventricular volume is maintained for only 80–200 ms, temporal resolution of MSCT may not have been sufficient in all patients.

Overall agreement of regional wall motion score was excellent; 91% of segments scored identically. The agreement for the individual wall motion scores was highest in the extremes, that is, in segments with either normal contractility (97%) or dyskinesia (92%), whereas it was slightly lower in segments showing intermediate contractile dysfunction. Because MSCT is most likely to be applied as a first-line screening tool, baseline left ventricular function may be used to fur-

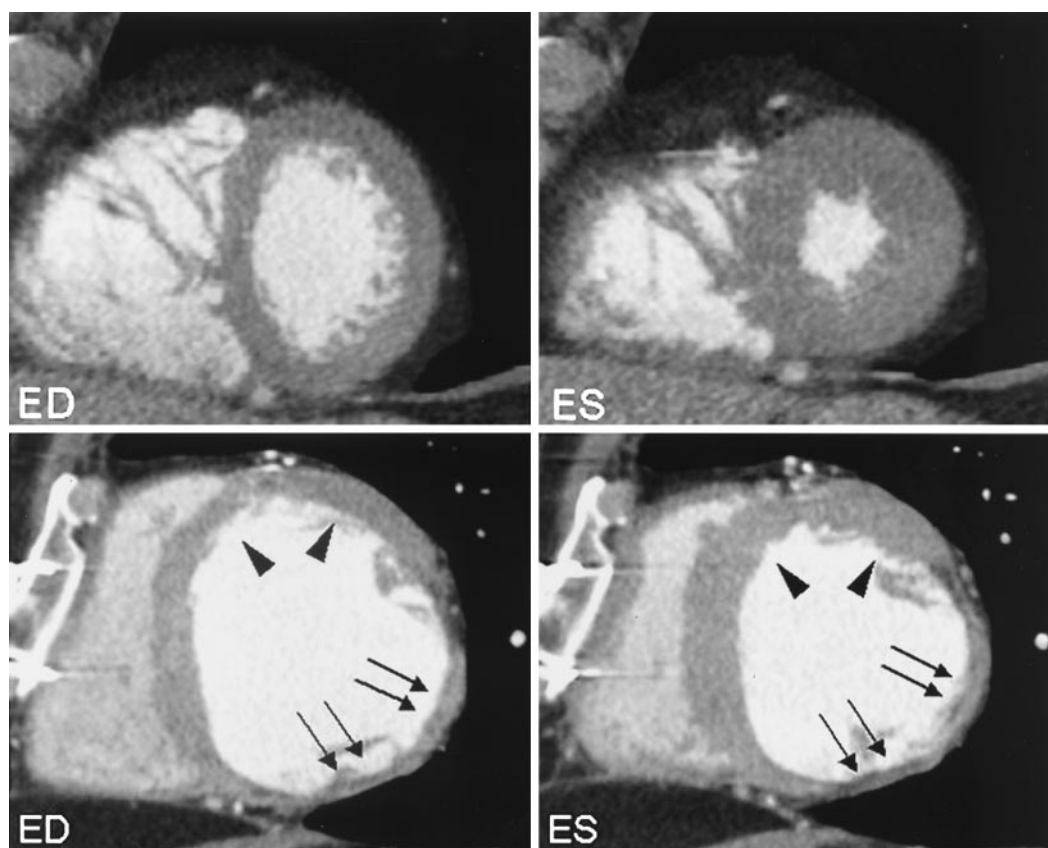


Figure 3—MSCT short-axis reconstructions in end diastole (left) and end systole (right). Upper panels: Normal systolic wall thickening is clearly present in all segments. Lower panels: Short-axis reconstructions of a patient with a previous inferolateral infarction are shown. Although preserved wall motion is still present in the anterior region (arrowheads), akinesia of the severely thinned wall is clearly visible in the infarcted region (arrows).

ther refine risk stratification in the individual patient. However, it currently does not offer an alternative to echocardiographic examination because evaluation of valvular or diastolic function is not possible with MSCT.

Some limitations of the current study must be acknowledged. First, in the present study, only 30 patients were included. Studies in larger patients cohorts are needed to precisely determine the accuracy of MSCT in patients with type 2 diabetes.

Second, left ventricular function analysis was compared with two-dimensional echocardiography instead of MRI, which is considered the current gold standard for evaluation of left ventricular function. In contrast to MRI, two-dimensional echocardiography relies on geometrical assumptions and may, therefore, be somewhat less accurate. Still, our results are very similar to those obtained in the few available comparisons between MSCT and MRI (13,14). Third, in the present study, 14% of coronary segments were uninterpretable, which is in line with previous studies (6,11,22). However, with the introduction of 32- and

64-slice systems, the percentage of uninterpretable segments is likely to decline further. Fourth, although some authors have recommended the use of β -blocking agents (7), no additional β -blocking agents were administered before the examination in the present study. The use of a multisegmented reconstruction algorithm, which is available on our MSCT equipment, allowed the inclusion of patients with heart rates >65 bpm without loss in temporal resolution (23). Furthermore, additional administration of β -blocking agents may have interfered with cardiac function analysis, rendering it less reliable. Finally, a major drawback of MSCT remains the radiation dose, which is ~ 6 – 9 mSv (24–26). The development of new filters and optimized acquisition protocols will lead to a substantial reduction of radiation dose.

In conclusion, accurate noninvasive evaluation of both the coronary arteries and left ventricular function with MSCT is feasible in patients with type 2 diabetes. This combined strategy may improve the noninvasive evaluation of CAD in this particular patient group.

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