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Multimodality Imaging of Anatomy and Function in Coronary Artery Disease

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Part II

Defining Patient Populations

II A

Coronary Risk Factors

Chapter 6

Non-Invasive Angiography and Assessment of Left Ventricular Function using Multi-slice Computed Tomography in Patients with Type 2 Diabetes

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Abstract

Background

Early identification of coronary artery disease (CAD) in patients with diabetes is important, since these patients are at elevated risk for developing CAD and have worse outcome as compared to non-diabetic patients, once diagnosed with CAD. Recently, non-invasive coronary angiography and assessment of left ventricular (LV) function has been demonstrated with multi-slice computed tomography (MSCT). The purpose of the present study was to validate this approach in patients with type 2 diabetes.

Methods

MSCT was performed in 30 patients with confirmed type 2 diabetes. From the MSCT images, coronary artery stenoses ($\geq 50\%$ luminal narrowing) and LV function (LV ejection fraction, regional wall motion) were evaluated and compared with conventional angiography and 2D-echocardiography.

Results

A total of 220 (86%) of 256 coronary artery segments were interpretable with MSCT. In these segments, sensitivity and specificity for the 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 LV ejection fractions demonstrated a mean difference of $-0.48\% \pm 3.8\%$ for MSCT and echocardiography, not significantly different from zero. Agreement between the 2 modalities for assessment of regional contractile function was excellent (91%, kappa statistic 0.81).

Conclusion

Accurate non-invasive evaluation of both the coronary arteries and LV function with MSCT is feasible in patients with type 2 diabetes. This non-invasive approach may allow optimal identification of high-risk patients.

Introduction

Type 2 diabetes is a major risk factor for coronary artery disease (CAD) and is associated with a 2- to 4- fold increase in the risk of developing CAD ¹. Furthermore, prognosis of patients with type 2 diabetes and confirmed CAD has been demonstrated to be worse than in non-diabetic patients with CAD. For example, the likelihood of developing myocardial infarction is significantly higher in diabetic patients with unstable angina compared to non-diabetic 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.

Non-invasive 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 since patients with diabetes frequently have diffuse, multi-vessel 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 non-invasive technique that is capable of direct visualization of the coronary arteries would be preferred. A promising new imaging technique for the non-invasive detection of CAD is multi-slice 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 (LV) function, which also is an important prognostic parameter ⁴. Although the studies on assessment of LV function with MSCT are scarce, the initial results demonstrated a good relation between LV ejection fraction assessed by MSCT and 2D-echocardiography or Magnetic Resonance Imaging (MRI) ¹²⁻¹⁴.

Combined assessment of LV function and the coronary artery status with MSCT may allow optimal non-invasive evaluation of patients with diabetes with suspected CAD. Thus far, the value of MSCT has not been evaluated in patients with diabetes. Accordingly, the purpose of the present study was to perform a combined assessment of coronary arteries and LV function in patients with type 2 diabetes using MSCT; the results were compared to conventional angiography and 2D-echocardiography, respectively.

Methods

Patients and study protocol

The study group consisted of 30 patients with known type 2 diabetes who were scheduled for conventional angiography because of anginal complaints. Criteria for the diagnosis of diabetes were, as recommended by the American Diabetes Association¹⁵:

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 2D-echocardiography was performed prior or after the CT examination within two 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 0.4s or 0.5s, 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, while the ECG was recorded simultaneously for retrospective gating of the data. To assess LV 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 cardiac software (MR Analytical Software System [MASS], Medis, Leiden, the Netherlands).

To evaluate the coronary arteries, 5 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, Minn. USA) for post-processing.

MSCT; Data analysis

Stenosis assessment was performed using a modified AHA-ACC segmentation model: the left main coronary artery (segment 5), the right coronary artery (segments 1, 2, 3, and if present 4 and 16), the left anterior descending coronary artery (segments 6,7, 8, and 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 prior to 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 model¹⁶. Each segment was assigned a wall motion score using a 4-point scale (1=normokinesia, 2=hypokinesia, 3=akinesia, and 4=dyskinesia). LV ejection fraction was calculated using semi-automated endocardial contour detection, with manual correction when necessary. Papillary muscles were regarded as being part of the LV cavity.

Conventional angiography

Conventional angiography was performed according to standard techniques. Vascular access was obtained by using the femoral approach with the Seldinger technique.

Coronary angiograms were visually evaluated by an experienced observer blinded to the MSCT data.

2D-echocardiography

Patients were imaged in the left lateral decubitus position using a commercially available system (Vingmed System FiVe/Vivid-7, GE-Vingmed, Milwaukee, WI, USA). 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 4-point scale as described above. LV ejection fractions were calculated from the 2- and 4-chamber images using the biplane Simpson's rule¹⁷.

Statistical analysis

Sensitivity, specificity, positive and negative predictive values for 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. Pre-test likelihood of CAD in patients without previous myocardial infarction or coronary bypass grafting was estimated using the Diamond-Forrester method¹⁸. Bland-Altman analysis was performed for each pair of values of LV ejection fraction to calculate limits of agreement and systematic error between the

two modalities¹⁹. Agreement for regional wall motion was expressed in a 4x4 table using weighted kappa statistics. A kappa value of <0.4 represents poor agreement, a kappa value between 0.4 and 0.75 fair to good agreement, and a kappa value of >0.75 is considered an excellent agreement, based on the Fleiss' classification²⁰. A p-value <0.05 was considered to indicate statistical significance.

Results

Patient characteristics

The patient characteristics are summarized in Table 1. The study group consisted of 30 patients (26 men, mean age 62 ± 10 years) with type 2 diabetes. The average duration of diabetes mellitus was 2.9 ± 4.4 years at the time of MSCT. A total of 11 patients received oral hypoglycaemic medication or insulin (n=5). Cardiac medication was continued during the study period. A total of 16 (53%) patients used beta-blocking agents, and no additional beta-blocking agents were administered in preparation of the scan.

Table 1. Clinical characteristics of the study population (n=30).

	n (%)
Gender (M/F)	26/4
Age (years)	62 ± 10
Beta-blocking medication	16 (53)
Heart rate during acquisition	69 ± 13
Diabetes type 2	30 (100)
Average HbA _{1c}	$6.9\% \pm 1.4\%$
Other risk factors for CAD	
Hypertension	16 (73)
Smoking	12 (56)
Hypercholesterolemia	21 (95)
Family with CAD	12 (56)
History	
Previous MI	20 (67)
Previous PCI/CABG	21 (70)/11 (37)
Vessel disease	
1-vessel	6 (20)
2-vessel	6 (20)
3-vessel	16 (53)
Angina Pectoris	
CCS class 1/2	7 (23)
CCS class 3/4	23 (77)
Heart Failure	
NYHA class 1/2	25 (83)
NYHA class 3/4	5 (17)

CABG: coronary artery bypass grafting; CCS: Canadian Cardiovascular Society; MI: myocardial infarction; NYHA: New York Heart Association; PCI: percutaneous coronary intervention.

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 4-slice MSCT, 18 (18%) were uninterpretable, whereas also 18 (11%) of 157 segments acquired with 16-slice MSCT were of non-diagnostic quality. Thus, 36 (14%) segments were classified 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. Thus, resulting sensitivity and specificity were 95%. When the uninterpretable segments were included in the analysis, resulting sensitivity and specificity were 81% and 82%, respectively.

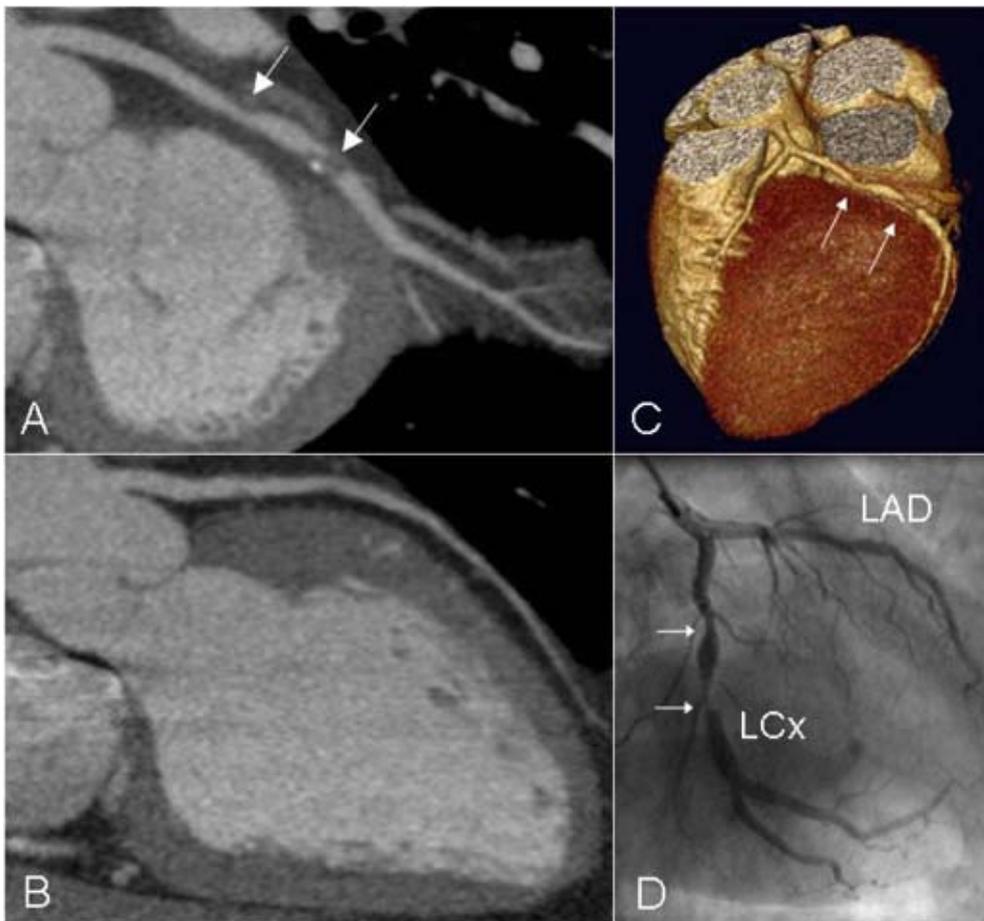


Figure 1. In panel A, a curved multiplanar reconstruction of a left circumflex coronary artery (LCx) with severe narrowing of the lumen is depicted. No abnormalities however were observed in the left anterior descending coronary artery (LAD) of this patient (panel B). Also, in the 3D volume rendered reconstruction (panel C), stenoses in the LCx as well as patency of the LAD are clearly visible. Findings were confirmed by conventional X-ray angiography (panel D).

A total of 21 grafts were present (arterial=5, venous=16). Conventional angiography revealed the presence of $\geq 50\%$ luminal narrowing in 9 grafts. MSCT correctly identified all 9 grafts with significant stenosis, whereas 9 of 12 grafts without significant stenosis were correctly identified on the MSCT images. In the 3 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 (87%) of 30 patients. In 7 patients, no significant abnormalities were observed during conventional angiography, and 5 (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 CAD was known. In the remaining 7 patients with suspected CAD, the pre-test likelihood according to Diamond-Forrester was intermediate in 2 and high in 5 patients. Conventional angiography demonstrated the presence of significant lesions in 5 patients, of which 4 (80%) were correctly identified with MSCT. Of the 2 patients without significant CAD, 1 (50%) was correctly assessed with MSCT.

Examples of MSCT images of both a stenotic and non-stenotic coronary artery with the corresponding angiographic images are shown in Figure 1.

LV function

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

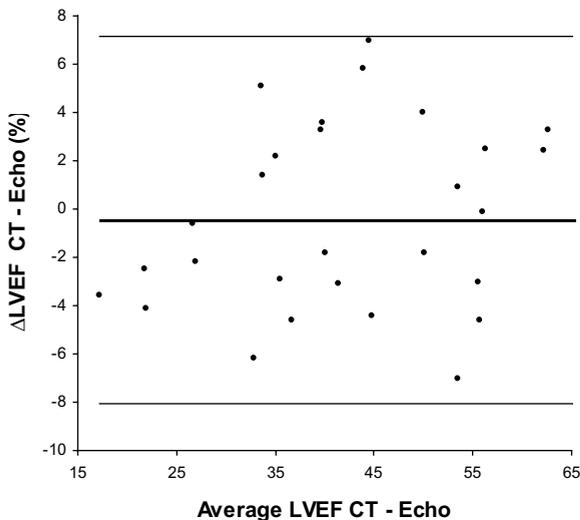


Figure 2. Bland-Altman plot in the comparison of MSCT and echocardiography in the assessment of LV ejection fraction.

The difference between each pair is plotted against the average value of the same pair (solid line= mean value of differences and dotted lines = mean value of differences ± 2 SDs).

Global function

Mean LV ejection fraction, as determined by echocardiography and MSCT, was $43\% \pm 14\%$ (range: 19% - 75%) and $43\% \pm 14\%$ (range: 15% - 72%, ns), respectively. Bland-Altman analysis in the comparison of CT and echo LV ejection fraction demonstrated a mean difference of $-0.48\% \pm 3.8\%$, not significantly different from zero (Figure 2).

Regional function

Echocardiography revealed contractile dysfunction in 157 (32%) of 493 segments, with 71 (45%) showing hypokinesia, 74 (47%) akinesia and 12 (8%) dyskinesia. In 149 (95%) of the dysfunctional segments, decreased systolic wall thickening was also observed on the MSCT images. An excellent agreement was shown between the two techniques, with 91% of segments scored identically on both modalities (kappa statistic 0.81 ± 0.03). Agreements for the individual gradings (1-4) were 97%, 82%, 73%, and 92%, respectively. In Figure 3, examples of short-axis reconstructions are shown, illustrating patients with and without wall motion abnormalities.

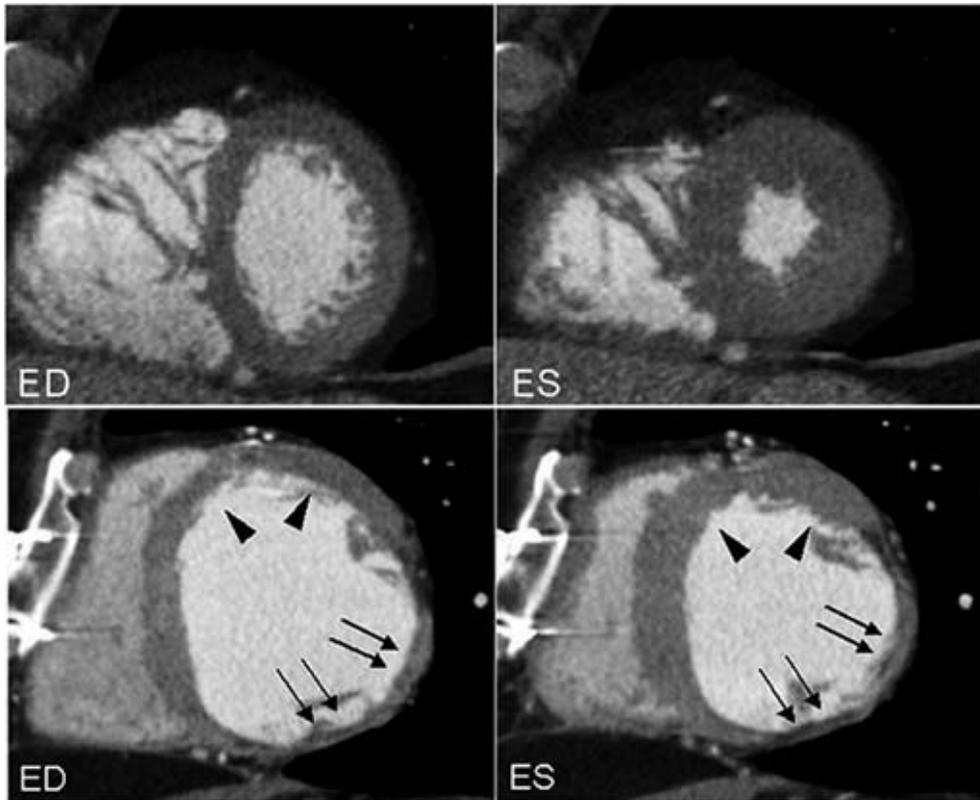


Figure 3. MSCT short-axis reconstructions in end-diastole (ED, left panels) and end-systole (ES, right panels). In the upper two panels (A), normal systolic wall thickening is clearly present in all segments. In the lower two panels, short-axis reconstructions of a patient with a previous inferolateral 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) (B).

Discussion

Our study demonstrates that non-invasive 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 finding, since clinical management is often difficult in patients presenting with diabetes and suspected CAD. In a substantial number of patients, non-invasive tests are inconclusive and knowledge of coronary anatomy (by means of invasive angiography) is often needed in order 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 prognostication 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, LV function analysis was performed after retrospective reconstruction of the acquired data. In the assessment of LV ejection fraction, a close correlation was observed between MSCT and 2D-echocardiography. Mean LV ejection fraction as determined by MSCT was slightly less as compared to the echocardiographic results, but no statistical difference was reached. A slight underestimation of LV ejection fraction with MSCT has been reported previously¹²⁻¹⁴ which may be attributed to an overestimation of LV end-systolic volume. Since 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 with 91% of segments scored identically. The agreement for the individual wall motion scores was highest in the extremes, i.e. in segments with either normal contractility (97%) or dyskinesia (92%), whereas it was slightly lower in segments showing intermediate contractile dysfunction. Since MSCT is most likely to be applied as a first line screening tool, baseline LV function may be used to further refine risk stratification in the individual patient. However, it does currently not offer an alternative to echocardiographic examination since evaluation of valvular or diastolic function is not possible with MSCT.

Some limitations of the current study need to 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, LV function analysis was compared to 2D-echocardiography instead of MRI, which is considered the current gold standard for evaluation of LV function. In contrast to MRI, 2D-echocardiogra-

phy relies on geometrical assumptions and may thus 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 beta-blocking agents⁷, no additional beta-blocking agents were administered prior to the examination in the present study. The use of a multi-segmented reconstruction algorithm, which is available on our MSCT equipment, allowed the inclusion of patients with heart rates higher than 65 beats per minutes without loss in temporal resolution²³. Furthermore, additional administration of beta-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 approximately 6-9 mSv²⁴⁻²⁶. The development of new filters and optimized acquisition protocols will lead to a substantial reduction of radiation dose.

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

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