Multimodality Imaging of Anatomy and Function in Coronary Artery Disease

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Chapter 10

Usefulness of 64-slice Multi-Slice Computed Tomography Coronary Angiography to assess In-stent Restenosis

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Abstract

Background

Recent investigations have shown increased image quality and diagnostic accuracy for non-invasive coronary angiography with 64-slice multi-slice computed tomography (64-slice MSCT) as compared to previous generations MSCT scanners, but data on the evaluation of coronary stents are scarce. The purpose of the present study was to evaluate the diagnostic accuracy of 64-slice MSCT coronary angiography in the follow-up of patients with previous coronary stent implantation.

Methods

In 182 patients (152 (84%) males, aged 58 ± 11 years) with previous stent (≥2.5mm diameter) implantation (n=192), 64-slice MSCT angiography using either a Sensation 64 (Siemens, Germany) or Aquilion 64 (Toshiba, Japan) was performed. At each center, coronary stents were evaluated by two experienced observers and evaluated for the presence of significant (≥50%) in-stent restenosis. Quantitative coronary angiography served as the standard of reference.

Results

A total of 14 (7.3%) stented segments were excluded because of poor image quality. In the interpretable stents, 20 of the 178 (11.2%) evaluated stents were significantly diseased, of which 19 were correctly detected by 64-slice MSCT. Accordingly, sensitivity, specificity and positive and negative predictive value to identify in-stent restenosis in interpretable stents were 95.0% (CI: 85% to 100%), 93.0% (CI: 90% to 97%), 63.3% (CI: 46% to 81%), and 99.3% (CI: 98% to 100%), respectively.

Conclusion

In-stent restenosis can be evaluated with 64-slice MSCT with good diagnostic accuracy. In particular a high negative predictive value of 99% was observed, indicating that 64-slice MSCT may be most valuable as a non-invasive method to exclude in-stent restenosis.

Introduction

Stent-implantation is increasingly performed in the treatment of significant coronary artery disease (CAD) and has significantly reduced the occurrence of restenosis as compared to balloon angioplasty [1;2]. Moreover, with the recent introduction of drug-eluting stents (DES), the occurrence of in-stent restenosis has further decreased [3-5]. Nonetheless, a subset of patients still presents with recurrent chest pain with possible in-stent restenosis and frequently evaluation with invasive coronary angiography is required.

A non-invasive alternative approach to evaluate these patients may be offered by 64-slice Multi-Slice Computed Tomography (MSCT). In native coronary arteries, sensitivities and specificities of approximately 90% and 96% [6-9] for detection of CAD have been reported, with a substantial gain in diagnostic accuracy over 4- and 16-slice MSCT. Also the evaluation of coronary stents, which posed still considerable problems with 4- and 16-slice MSCT [10], may have improved with 64-slice MSCT. However, few data are currently available and the routine use of MSCT in patients with a history of stent implantation is at present not recommended [11;12]. The purpose of the present study was to evaluate the diagnostic performance of 64-slice MSCT to identify in-stent restenosis (and occlusion) in comparison to the gold standard, invasive coronary angiography.

Methods

Study population

The study population consisted of 182 patients who were referred for invasive coronary angiography after previous coronary stent (≥2.5 mm diameter) implantation. Referral of patients for invasive coronary angiography was partially part of an ongoing protocol and partially routine (based on the presence of symptoms, abnormal exercise ECG and/or ischemia on myocardial perfusion imaging). In addition to invasive coronary angiography, 64-slice MSCT was performed. Exclusion criteria were the following: 1) atrial fibrillation, 2) renal insufficiency (serum creatinine >120 mmol/L), 3) known allergy to iodine contrast media, 4) pregnancy and 5) coronary stent diameter <2.5 mm. The study was approved by the ethical committee of the different centers, and all participating patients gave informed consent.

Scan protocol and image reconstruction

MSCT angiography was performed with 2 different 64-slice MSCT scanners (Sensation 64®, Siemens, Germany, n=150, and Aquilion 64, Toshiba Medical Systems, Japan, n=32). Thirty-four patients (19%) had a pre-scan heart rate ≥65 beats per minute, and were given a single oral dose of 100 mg metoprolol one hour before the examination in the absence of contraindications. A bolus of 100 ml iomeprol (400 mgI/ml; Iomeron®, Bracco) was intravenously injected (4-5 ml/s) followed by 50 ml of

saline at the same rate using a double-head injector (Stellant, MedRAD, Pittsburgh, USA). To trigger the start of the scan a real-time bolus tracking technique was used [13]. During the scan which was performed during an inspiratory breath hold of 8 s to 12 s the MSCT data and ECG trace were acquired. Scan parameters were (for Siemens and Toshiba, respectively): individual detector collimation 32 x 2 x 0.6 mm and 64 x 0.5 mm, tube voltage 120 kV for both, mAs 900 and 712, gantry rotation time 330 ms and 400 ms. No ECG-pulsing was used.

Reconstruction parameters (for Siemens and Toshiba, respectively): effective slice width 0.75 mm and 0.5 mm, increment 0.4 mm and 0.3 mm, standard and sharp heart view convolution filters for both. For Siemens, B30f and B46f were used, whereas for Toshiba, Q04 was used in addition to Q05-Q07.

Synchronized to the recorded ECG, axial slices were reconstructed from the acquired MSCT data with the use of segmented or half reconstruction algorithms.

Image data sets were reconstructed during the mid-to-end diastolic phase, during which coronary artery displacement is relatively small, with reconstruction window positions starting at 400 ms before the next R wave and/or at 75% of the R-to-R interval. If indicated, additional temporal window positions were explored including the end-systolic phase to obtain images with least motion artefacts.

MSCT image interpretation

At each center two observers, both blinded to angiographic and clinical findings but aware of previous cardiac history, evaluated the MSCT examinations using axial slices, multiplanar and curved reconstructions. Of note, different window settings, including 1500/300 HU were used for optimal stent assessment.

A stent was judged to be occluded when the lumen inside the stent was darker than the contrast-enhanced vessel before the stent and/or when no run-off could be visualised at the distal end of the stent [14;15].

Non-occlusive in-stent re-stenosis was considered when the lumen inside the stent showed a darker rim (eccentric or concentric) between the stent and the enhanced vessel lumen with a lumen reduction ≥50% (as compared to other portions of the stent). In addition, the presence of reduced run-off distal to the stent was taken into consideration; if reduced distal run-off was observed, this was found to be suggestive of in-stent restenosis. Importantly, the presence of distal run-off was not used as a criterium for the absence of significant in-stent restenosis, since collateral filling may occur (which cannot be detected adequately by MSCT). In Figures 1, 2 and 3, examples are provided of patent and diseased stents.

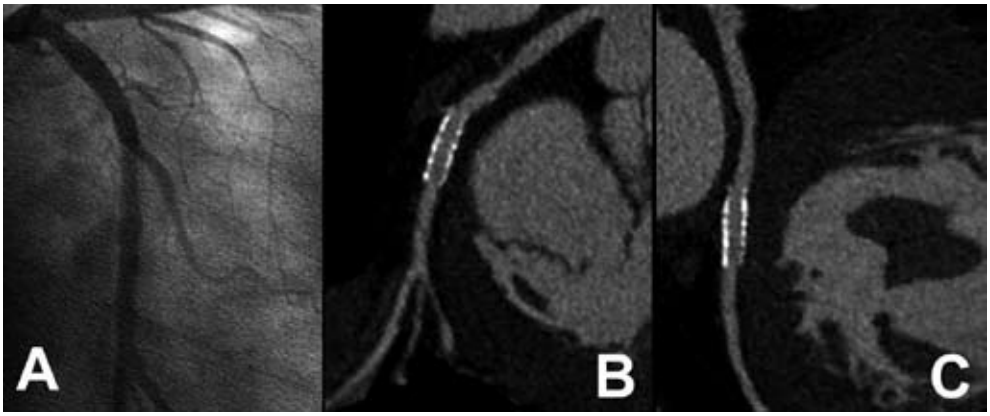

Figure 1. Example of a patent stent.
Conventional coronary angiography (Panel A) demonstrated patency of a stent (Cypher, 3.0 x 18 mm) placed in the left circumflex coronary artery. In Panels B and C two orthogonal curved multiplanar reconstructions obtained with 64-slice MSCT (Siemens Sensation, kernel B46f) are provided, also demonstrating patency of the stent.

Invasive coronary angiography

Conventional selective coronary angiography was performed with standard techniques and evaluated by a reviewer blinded to the MSCT results with the use of quantitative coronary angiography systems (CAAS II, Pie Medical, Maastricht, The Netherlands or QCA-CMS version 6.0, Medis, Leiden, The Netherlands). The diameter stenosis, as a percentage of the reference diameter, was determined in two orthogonal directions and the average between these two values determined the stenosis severity.

Statistical analysis

Sensitivity, specificity, positive and negative predictive values (including 95% confidence intervals (CI)) for the detection of in-stent restenosis ≥50% using conventional angiography in combination with QCA as the gold standard, were calculated. All statistical analyses were performed using SPSS software (version 12.0, SPSS Inc, Chicago, Il, USA). A value of $P<0.05$ was considered statistically significant.

Results

Patient characteristics

In total, 182 patients (152 males, aged 57.8 ± 10.6 years) with a total of 192 coronary stents were enrolled in the study. A total of 4 patients were not enrolled due to the presence of stents with a diameter <2.5 mm. Also, 5 patients were not studied due to a high heart rate in combination with beta-blocker intolerance. Baseline characteristics of the study population are provided in Table 1.

The average time interval between stent implantation and 64-slice MSCT coronary angiography was 6.2 ± 1.6 months; 64-slice MSCT and conventional angiography were performed within 1 month of each other (average 9 ± 8 days); MSCT was always performed first. The site of stent implantation was: right coronary artery (RCA) in 55 (28.6%), left main coronary (LM) in 11 (5.7%), left anterior descending (LAD) in 113 (58.9%), and left circumflex (LCx) in 13 (6.8%). Average stent diameter was 3.1 ± 0.4 mm (range 2.5 mm to 4.5 mm), whereas stent length ranged from 8.0 mm to 33 mm (average 18 ± 7 mm). Eight different stent types were evaluated, the non-DES stents being Vision (Guidant), Driver (Medtronic), Ave S7 (Medtronic), Orbus (Orbus technologies), Bx Velocity (Cordis), and Liberté (Boston Scientific). Included DES-stents were Cypher (Cordis) and Taxus (Boston Scientific). Average heart rate during MSCT data acquisition was 60 ± 7.9 beats per minute.

Table 1. Demographic and angiographic characteristics of patients (n=182).

	n (%)
Age (yrs)	57.8±10.6
Males	152, 84%
Previous myocardial infarction	94, 52%
Previous PCI	182, 100%
Body mass index (kg/m^2)	28.8 ± 3.8
Diabetes mellitus type II	23, 13%
Hypercholesterolemia	64, 35%
Hypertension	57, 31%
Family history of CAD	88, 48%
Current smoking	110, 60%
Angiography	
1-vessel disease	134, 72.5%
2-vessel disease	34, 18.7%
3-vessel disease	16, 8.8%
Stent location	
RCA	55, 28.6%
LM	11, 5.7%
LAD	113, 58.9%
LCx	13, 6.8%

Abbreviations: CAD: coronary artery disease; LAD: left anterior descending coronary artery, LCx: left circumflex coronary artery; LM: left main coronary artery; PCI: percutaneous coronary intervention.

Coronary stent analysis

In total, 178 stents were available for evaluation while 14 stents (7.3%) were considered uninterpretable due to residual motion and high-density artefacts (Table 2). No significant differences were observed in interpretability between the different stent diameters; 3 (5.8%) of 52 stents with a diameter <3.0 mm were uninterpretable, whereas 7 (10%) of 70 and 4 (5.7%) of 70 stents with diameter of respectively 3.0 mm or >3.0 mm were uninterpretable (Table 3).

The incidence of significant in-stent restenosis (non-occlusive in-stent restenosis and total stent occlusions) was 11.2% (20/178), as determined by conventional angiography. Examples of patent as well as stents with significant in-stent restenosis are provided in Figures 1, 2, and 3, respectively.

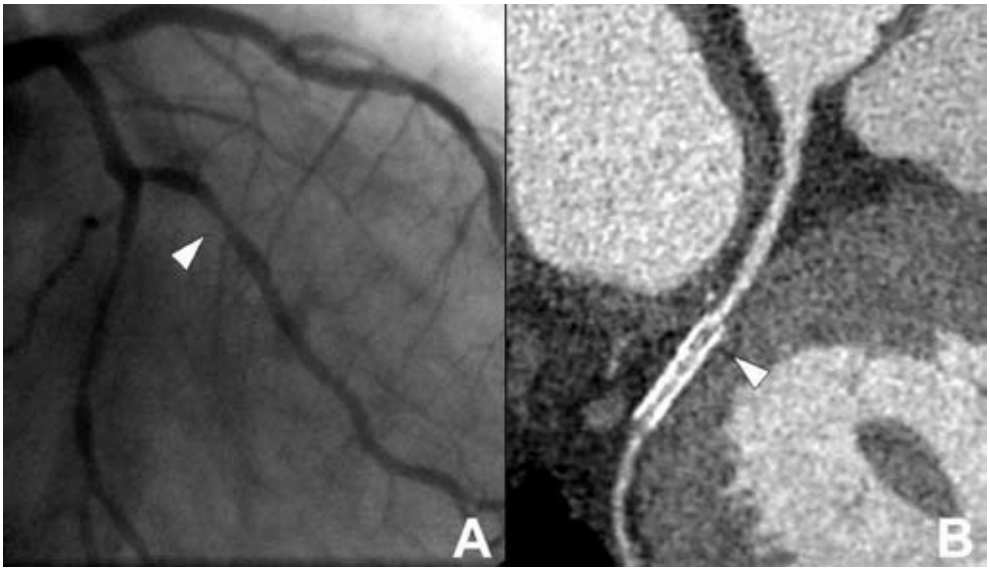

Figure 2. Example of in-stent restenosis.
Conventional coronary angiography (Panel A) revealed in-stent restenosis in a stent (Taxus, 2.5 x 20 mm) placed in the second marginal branch of the left circumflex coronary artery (arrowhead). In Panel B, a curved multiplanar reconstruction obtained with 64-slice MSCT (Siemens Sensation, kernel B46f) is provided. In the proximal part of the stent (arrowhead), a hypodense area can be observed, indicating the presence of in-stent restenosis.

All 7 stent occlusions were correctly identified by 64-slice MSCT, whereas 1 stent (located in the second diagonal) of 13 stents with significant but non-occlusive in-stent restenosis remained undetected by MSCT. Of the 158 stents without significant in-stent restenosis, 147 were correctly evaluated by 64-slice MSCT, whereas 11 stents were incorrectly considered positive. Accordingly, the overall sensitivity, specificity, positive and negative predictive value to detect significant in-stent restenosis were 95.0% (19/20, CI: 85% to 100%), 93.0% (147/158, CI: 90% to 97%), 63.3% (19/30, CI: 46% to 81%), and 99.3% (147/148, CI: 98% to 100%), respectively. More detailed information is depicted in Table 2. In stents without significant stenosis on conventional angiography, average percentage stenosis as determined by QCA was significantly higher in stents falsely classified positive on MSCT as compared to stents correctly classified negative (36% versus 25%, $P<0.05$). Similarly, average percentage stenosis was lower in stents false negative on MSCT as compared to correct positive stents (65% versus 73%, P=NS).

In a subanalysis, the rate of false diagnosis was evaluated according to stent diameter. In stents with a diameter <3.0 mm, 3 (6.1%) of 49 stents were incorrectly diagnosed. For stents with a diameter of 3.0 mm, this percentage was 1.6% (1 of 63), while in stents with a diameter >3.0 mm incorrect diagnosis was obtained with MSCT in 8 of 66 (12.0%). More details on the rate of false positives and negatives

are provided in Table 3. In Table 4, the results from the 2 scanners from the 2 centers are reported separately. At the Leiden center, relatively more stents were deemed uninterpretable as compared to the Rotterdam center (14.3% versus 5.3%, P=NS). Diagnostic accuracy was slightly lower in the Rotterdam center (91.5% versus 100%, P<0.05). However, when all stents (including the uninterpretable stents) were included in the analysis, no significant differences were observed.

Table 2. Diagnostic accuracy of 64-slice MSCT to detect significant in-stent restenosis.

	≥ 50% in-stent restenosis
Assessable	178/192 (92.7%, 89% to 97%)
With uninterpretable stents excluded	
Sensitivity	19/20 (95.0%, 85% to 100%)
Specificity	147/158 (93.0%, 90% to 97%)
Positive predictive value	19/30 (63.3%, 46% to 81%)
Negative predictive value	147/148 (99.3%, 98% to 100%)
With uninterpretable stents included	
Sensitivity	19/21 (90.5%, 78% to 100%)
Specificity	147/171 (86.0%, 81% to 92%)
Positive predictive value	19/43 (44.2%, 29% to 59%)
Negative predictive value	147/149 (98.7%, 97% to 100%)

Values are segments (%, 95% CI).

Discussion

In the present study, a sensitivity and specificity of respectively 95% and 93% were observed for the non-invasive detection of coronary in-stent restenosis. In addition, a negative predictive value of 99% was observed, suggesting that 64-slice MSCT may allow reliable exclusion of in-stent restenosis prior to more invasive procedures such as conventional coronary angiography.

During MSCT imaging, visualization of stents is particularly challenging because of the metallic struts resulting in "blooming artefacts" [16]. Accordingly, the stent wall appears enlarged on the MSCT images, which in turn affects the capability to visualize the in-stent lumen. The extent of this artefact depends on the material and design of the stent with more severe artefacts in stents with high metal content. While this effect is of minor or no importance in large vessels, such as the aorta and its abdominal branches, it can considerably impair the visualization of the lumen in smaller vessels such as the coronary arteries [16].

Not surprisingly therefore, visualization of stent lumen could not be achieved in preliminary investigations using 4-slice MSCT scanners [10]. In a more recent report 16-slice MSCT was applied, resulting in a sensitivity and specificity of 78% and 100% [15]. Nonetheless, 15 (23%) of the 65 included stents were uninterpretable, indicating still a limited value for MSCT coronary angiography in populations with previous stent implantation [15]. More detailed analysis of these 15 uninterpretable stents revealed that stent assessability appears to be highly dependent on stent type and size in particular. These observations were further underlined by Gilard and colleagues [17] who showed in 143 patients

undergoing 16-slice MSCT, an increase of stent interpretability from 51% for stents ≤ 3.0 mm to 81% when only stents >3.0 mm were included. More recently, data on stent evaluation using more advanced MSCT technology were reported by Gaspar et al [18], who evaluated 65 patients with 111 implanted coronary stents using 40-slice MSCT. A considerable improvement in image quality was witnessed in this study, since only a small number of stents (n=5, 5%) were of non-diagnostic image quality. Considering these 5 stents as having restenosis, the authors reported a sensitivity and specificity for detection of in-stent restenosis of 89% and 81% respectively.

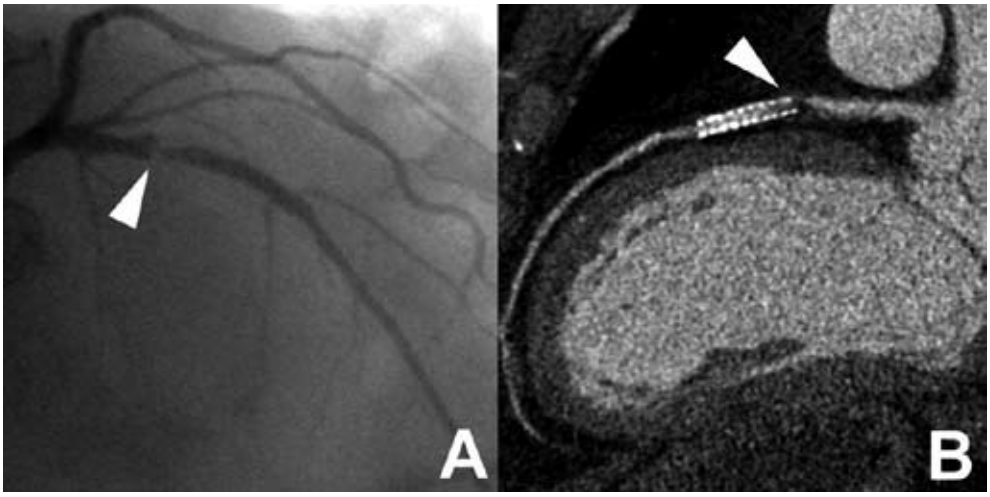

Figure 3. Example of high-grade in-stent restenosis.
In Panel A, a conventional coronary angiogram is provided demonstrating the presence of high-grade in-stent restenosis in the proximal part of a stent (Taxus, 3.0 x 24 mm) placed in the left anterior descending coronary artery (arrowhead). Also Panel B, a curved multiplanar reconstruction obtained with 64-slice MSCT (Siemens Sensation, kernel B46f), shows the presence of a large obstructing hypodense lesion in the proximal part of the stent (arrowhead), indicating the presence of high-grade in-stent restenosis.

These observations are further underlined by the first ex vivo reports on stent evaluation with 64-slice MSCT, suggesting further improvement in stent visibility as well a reduction of artificial lumen narrowing as compared to 16-slice MSCT [19;20]. Also in vivo promising results were reported using 64-slice MSCT by Rist et al, who could evaluate 45 (98%) of 46 stents with a sensitivity and specificity of 75% and 92%, respectively [21]. Nonetheless, somewhat discouraging results were recently reported by Rixe et al [22], who performed 64-slice MSCT in 64 patients with 102 previously implanted stents. Similar to our study, 64-slice MSCT was shown to be highly accurate with reported sensitivity and specificity of 86% and 98%, respectively. However, evaluation could be performed in only 58% of stents, indicating a major limitation of the current technique. In contrast, only 7% of stents were deemed uninterpretable in our present study. To a large extent this discordance may be due to differences in image interpretation. In our present study evaluation was performed with the intention to diagnose in order to allow generalization of results as much as possible to daily clinical routine. Thus, only stents with severely degraded image quality were excluded. In contrast, a more stringent

approach was performed by Rixe et al, and in their study, stents were deemed uninterpretable in the presence of any artifact, albeit small. Importantly, both in their study as well as ours, a high negative predictive value was obtained (98% and 99%, respectively), implying a potential role for MSCT to exclude in-stent restenosis in patients presenting with chest pain after stent implantation.

Table 3. Relationship between stent size and accuracy.

	Stent diameter		
	<3.0 mm	**3.0 mm**	**>3.0 mm**
Assessable	49/52 (94.2%, 88% to 100%)	63/70 (90.0%, 83% to 97%)	66/70 (94.3%, 89% to 100%)
False positive	2/49 (4.1%, 0% to 9.7%)	1/63 (1.6%, 0% to 4.7%)	8/66 (12%, 4.2% to 19.8%)
False negative	1/49 (2.0%, 0% to 5.9%)	0/63 (0%, NA)	0/66 (0%, NA)

Values are segments (%, 95% CI).
NA: not applicable.

Limitations

Several limitations should be addressed. First, only patients having stents with a diameter ≥2.5 mm were included, whereas stents <2.5 mm, which may be encountered in 3% to 5% of patients with previous stent placement, were excluded, as at present, they cannot be accurately evaluated with MSCT. Accordingly, the results obtained in the present study may not be generalizable to other population with different stent characteristics.

Second, as previously reported with MSCT coronary angiography, only patients with stable and low heart rates were included in this study and a high percentage received additional β-blockers to further reduce heart rate. Accordingly, the results of the present study may not apply to the general population, as in addition to patients with smaller stents, also patients with atrial fibrillation and contra-indications to β-blocking medication were not studied. Third, in-stent restenosis was only present in a small number of stents (11%). However, the findings reflect the current clinical situation, with low in-stent restenosis rates [3-5]. In addition, data acquisition was performed in 2 different centers using 2 different 64-slice MSCT systems which may have influenced the results. Also, no data on interobserver variability were available. Finally, several disadvantages are inherent to the technique itself, including the high radiation exposure (15 to 20 mSv) [23;24] and use of iodinated contrast which remain a matter of concern for routine use of this technique. Also, an important limitation of MSCT remains the fact that only anatomical information is obtained, whereas the presence or absence of ischemia cannot be established from the MSCT images. Accordingly, in patients with significant restenosis, functional testing remains mandatory to determine further management.

Table 4. Results from the 2 scanners from the 2 centers separately.

	Rotterdam Siemens Sensation 64-slice	Leiden Toshiba Aquilion 64-slice
Assessable	142/150 (94.7%, 91% to 99%)	36/42 (85.7%, 76% to 96%)
Sensitivity	15/16 (93.8%, 82% to 100%)	4/4 (100%)
Specificity*	115/126 (91.3%, 86% to 96%)	32/32 (100%)
Positive predictive value*	15/26 (57.7%, 39% to 77%)	4/4 (100%)
Negative predictive value	115/116 (99.1%, 97% to 100%)	32/32 (100%)
With uninterpretable stents included		
Sensitivity	15/17 (88.2%, 82% to 100%)	4/4 (100%)
Specificity	115/133 (86.5%, 80% to 92%)	32/38 (84.2%, 72% to 96%)
Positive predictive value	15/33 (45.5%, 28% to 62%)	4/10 (40.0%, 10% to 70%)
Negative predictive value	115/117 (98.3%, 95% to 100%)	32/32 (100%)

Values are segments (%, 95% CI).
* P<0.05 between 2 centers

Conclusion

In-stent restenosis can be evaluated with 64-slice MSCT with good diagnostic accuracy. In particular, a high negative predictive value of 99% was observed, indicating that 64-slice MSCT may be most valuable to exclude in-stent restenosis.

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Chapter 11

Evaluation of Patients with Previous Coronary Stent Implantation using 64-slice Multi-Slice Computed Tomography

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Abstract

Background

To prospectively evaluate the diagnostic accuracy of 64-slice Multi-Slice Computed Tomography (MSCT) for the assessment of in-stent or peri-stent restenosis, using conventional coronary angiography as the reference standard.

Methods

The study was approved by the medical ethics committee and informed consent was obtained in all 50 (40 men, mean age 60 ± 11 years) enrolled patients. In addition to conventional coronary angiography with quantitative coronary angiography (QCA), 64-slice MSCT was performed. For each stent, assessability was determined and related to stent characteristics and heart rate using Chi-Square. In the interpretable stents and peri-stent lumina (5.00mm proximal and distal to the stent), the presence of significant (≥50%) restenosis was determined. For this analysis, partially overlapping stents were considered as a single stented segment.

Results

Of 76 stents, 65 (86%) were determined assessable. Increased heart rate and overlapping positioning were found to be associated with increased stent uninterpretability ($P<0.05$), whereas stent location or strut thickness were not. In 7 patients stents were placed overlapping resulting in 58 stented segments available for the evaluation of significant (≥50%) in-stent restenosis. All 6 significant (≥50%) in-stent restenoses were detected and the absence of significant (≥50%) restenosis was correctly identified in the 52 remaining stented segments, resulting in a sensitivity and specificity of 100%. Sensitivity and specificity for the detection of significant (≥50%) peri-stent stenosis were 100% and 98%, respectively.

Conclusion

In selected patients with previous stent implantation, sensitivity and specificity of 100% to detect significant (≥50%) in-stent restenosis and 100% and 98%, respectively, to detect significant (≥50%) peri-stent stenosis were observed for 64-slice MSCT.

Introduction

Currently, follow-up imaging in patients presenting with recurrent symptoms after previous intracoronary stent placement is performed by means of conventional coronary angiography. However, this is an invasive procedure associated with a small but definite risk of serious complications [1;2]. Considering the fact that a substantial number of procedures are not followed by an intervention, a non-invasive diagnostic procedure capable of evaluating not only native coronary arteries but also coronary stents would therefore be of great benefit.

Although promising results have been obtained using Multi-Slice Computed Tomography (MSCT) for the detection of coronary artery stenoses in native coronary arteries [3-5], evaluation of metallic stents has not been as promising [6-10]. While substantial improvement in image quality and diagnostic accuracy was observed with 16-slice as compared to 4-slice MSCT systems, still relatively high numbers of stents with inadequate image quality were reported. In particular, stents with thicker struts or smaller diameters tended to suffer from degraded image quality [6;7;9].

Recently, 64-slice MSCT systems have become available and studies evaluating coronary stent assessment *in vitro* using 64-slice MSCT suggest further improvement in image quality [11;12]. However, only limited data with 64-slice MSCT are available in patients thus far with conflicting results, as a percentage interpretable stents of 58% was recently reported by Rixe et al. [13]. Thus, the purpose of this study was to prospectively evaluate the diagnostic accuracy of 64-slice MSCT for the assessment of in-stent or peri-stent restenosis, using conventional coronary angiography as the reference standard.

Methods

Patients

The study group consisted of 50 consecutive patients (40 men, mean age 60 ± 11 years, range 41 to 79 years) who met our criteria and who had previously undergone percutaneous transluminal coronary angioplasty (PTCA) treatment in combination with stent placement. Patients were scheduled for diagnostic conventional coronary angiography from June 2005 to May 2006. In addition, MSCT coronary angiography was performed to allow non-invasive evaluation of the presence of in-stent restenosis or occlusion. Exclusion criteria were the following: 1) atrial fibrillation, 2) renal insufficiency (serum creatinine >120 mmol/L), 3) known allergy to iodine contrast media, and 4) pregnancy. All patients were on continuous beta-blocker medication, and no additional beta-blockers were administered prior to MSCT (Table 1). On average, MSCT was performed 13.4 ± 13.3 months (range 1 – 66 months) after stent implantation.

Conventional coronary angiography in combination with quantitative coronary angiography (QCA) analysis was performed on average 14 ± 9 days after MSCT and served as reference standard. All patients gave informed consent to the study protocol, which was approved by the ethics committee of the Leiden University Medical Center, after the study details, including radiation exposure, were explained.

Table 1. Clinical characteristics of the study population (n=50).

	n (%)
Gender (M/F)	40/10
Age (years)	60 ± 11
Heart Rate (bpm)	58 ± 10
Single vessel disease	22 (44%)
Multi-vessel disease	28 (56%)
Previous myocardial infarction	46 (92%)
Anterior	31 (67%)
Inferior	14 (30%)
Both	1 (2%)
Previous PTCA	50 (100%)
Previous CABG	0 (0%)
Stent location	
LM	0 (0%)
LAD	36 (47%)
LCx	11 (14%)
RCA	29 (38%)

Values are n (%).
Bpm: beats per minute; CABG: coronary artery bypass grafting; LM: Left main coronary artery; LAD: Left anterior descending coronary artery; LCx: Left circumflex coronary artery; RCA: Right coronary artery.

Stent characteristics

Diameter of implanted stents ranged from 2.25 to 4.0 mm with an average of 3.4 ± 0.3 mm, while stent length ranged from 8.0 mm to 33.0 mm with an average of 19.4 ± 5.0 mm. In total, 21 stents were positioned with partial overlap. Ten different stent types were evaluated, of which the majority were non-drug-eluting stents (DES): Vision (Guidant, n=33), Driver (Medtronic, n=3), Ave S7 (Medtronic, n=2), Ave S670 (Medtronic, n=1), Orbus (Orbus technologies, n=2), Tristar (Guidant, n=2), Bx Velocity (Cordis, n=1), and Liberté (Boston Scientific, n=1). In addition, 31 DES-stents (Cypher, Cordis, n=30 and Achieve, Guidant, n=1) were included.
Of these stents, Cypher, Bx Velocity and Tristar were considered to have thick struts (≥140 μm).

Data acquisition

Multi-Slice Computed Tomography

MSCT was performed using a Toshiba Multi-slice Aquilion 64 system (Toshiba Medical Systems, Tokyo, Japan) with a collimation of 64 x 0.5 mm and a rotation time of 0.4, 0.45 or 0.5 s, depending on the heart rate. The tube current was 350 mA, at 120 kV. Non-ionic contrast material was administered in the antecubital vein with an amount of 90-105 ml, depending on the total scan time, and a flow rate of 5.0 ml/sec (Iomeron 400 ®). Repetitive low-dose monitoring examinations (120 kV, 10 mA) were performed 5 seconds after the start of contrast medium injection. After the preset contrast enhancement threshold level of baseline HU + 100 HU in the descending aorta was reached, the MSCT

examination was automatically initiated. After a 2 second delay, data acquisition was performed during an inspiratory breath hold of approximately 10 seconds, while the ECG was recorded simultaneously to allow retrospective gating of the data.

For evaluation of the coronary arteries and intracoronary stents, data were reconstructed using a segmented reconstruction algorithm at 75% of the R-R interval with a slice thickness of 0.5 mm and a reconstruction interval of 0.3 mm. If motion artefacts were still present in this phase, additional reconstructions were explored to obtain the reconstruction phase with least motion artefacts (23 patients). For this purpose, images were reconstructed at a single level throughout the R-R interval in steps of 20ms to obtain information on the individual patient's pattern of cardiac motion. Based on these images, the time point to reconstruct the entire data set was chosen. Also, in all patients, an additional data set was reconstructed in the most optimal phase(s) using a sharper reconstruction kernel (Q04 instead of Q05-07) to improve stent image quality [14]. MSCT was performed successfully in all patients. Average heart rate during the acquisition was 58 ± 10 (range 38 to 86).

Conventional coronary angiography

Conventional coronary angiography was performed according to standard techniques by 2 experienced operators with respectively 10 and 15 years experience. Vascular access was obtained using the femoral approach with the Seldinger technique and a 6- French catheter.

Data analysis

Multi-Slice Computed Tomography

For each individual coronary artery, the data set containing no or the least motion artifacts was transferred to a dedicated workstation (Vitrea2, Vital Images, Plymouth, Minn. USA) for post-processing.

Coronary stents were evaluated on both the standard kernel and sharper kernel reconstructions using predominantly the original axial MSCT images, while manually obtained curved multiplanar reconstructions were used for verification of findings. 3D volume rendered reconstructions were not used. In addition, the axial images and curved multiplanar reconstructions were viewed in 3 different window and level settings; 1000/200 HU as a standard window level while also window levels of 1600/300 HU and 2500/900 HU were used to improve stent appearance. Assessment was performed blinded to the conventional coronary angiography results in consensus reading by 2 experienced observers, both having 3.5 years experience in the evaluation of MSCT coronary angiography, with one also having extensive (15 years) experience in conventional coronary angiography and intervention.

First, each individual stent was assigned an image quality score of: 1 (good image quality, no artifacts), 2 (moderate image quality, minor or moderate artifacts present but diagnosis possible) or 3 (uninterpretable, no diagnosis possible) as previously described [9;15]. Also, it was documented whether stents were positioned partially overlapping or not. If so, the stents were consequently considered as a single stented segment for the evaluation of in-stent or peri-stent stenosis.

Subsequently, the presence of significant restenosis (≥50% reduction of lumen diameter) was as-

sessed for each stented segment, while also the observation of non-significant (<50% reduction of lumen diameter) neo-intima hyperplasia within the stented segment was documented. Finally, since restenosis of the stent borders may also regularly occur, the presence of peri-stent stenosis, ≥50% narrowing of luminal diameter 5.00 mm proximal and distal to the stented segment was also evaluated as previously described [9].

Conventional and quantitative coronary angiography

Conventional angiograms were evaluated in consensus by two experienced observers without knowledge of the MSCT data. First, the location of the intracoronary stents was identified on the images before contrast injection. Subsequently, QCA with automated vessel contour detection after catheter-based image calibration was performed in end-diastolic frames by 2 qualified observers with respectively 2 and 10 years experience in QCA using a standard algorithm dedicated for stent analysis (Brachy-DES analysis, QCA-CMS version 6.0, Medis, Leiden, The Netherlands) [16]. QCA was performed of the stented segment as well as its proximal and distal (5.00 mm) lumina and percentage diameter reduction was determined. An in-stent lumen diameter narrowing ≥50% in diameter (up to in-stent occlusion) was defined as a significant restenosis.

Statistical analysis

Continuous variables are presented as means ± one standard deviation (SD), whereas categorical data are summarized as frequencies and percentages. In order to relate stent assessability to stent characteristics, stents were divided according to location in the coronary tree and according to strut thickness (with stents with ≥140 μm struts regarded as having thick struts and stents with <140 μm struts regarded as having thin struts), as previously described [9]. Distinction was also being made between stents positioned partially overlapping or not. Percentage assessable stents was calculated for each category and compared using Chi-Square analysis with Yates' correction. In addition, average heart rate was compared between interpretable stents and stents uninterpretable due to attenuation artefacts or motion artefacts using the Student's *t* test for independent samples. Logistic regression analyses were applied to correlate segment and patient characteristics to image quality, using the generalized estimating equation (GEE) method developed by Liang and Zeger [17]. Two (dichotomous) outcome variables were considered: good versus moderate-or-uninterpretable image quality, and good-or-moderate quality versus uninterpretable image quality. The GEE analyses were performed with proc GENMOD with a binominal distribution for the outcome variable, the link function specified as logit, and patients as separate subjects. Odds ratios and 95% confidence intervals (CI) are reported. Sensitivity, specificity, positive and negative predictive values (including 95% confidence intervals) for the detection of in-stent restenosis ≥50%, as determined by conventional angiography in combination with QCA, were determined for each stented segment. In addition, diagnostic accuracy was also determined for the detection of significant (≥50%) narrowing of the peristent lumina (5.00 mm proximal and distal to the stented segment).

Table 2. Results from GEE analysis

	Odds Ratio (95% CI)
Good versus moderate-or-uninterpretable image quality	
Heart rate*	0.98 (0.93-1.05)
Overlapping (Y/N)	0.70 (0.17-2.96)
Strut Thickness (≥140μm or <140μm)	0.44 (0.15-1.29)
Good-or-moderate versus uninterpretable image quality	
Heart rate*	0.94 (0.86-1.03)
Overlapping (Y/N)	0.16 (0.03-0.87)
Strut Thickness (≥140μm or <140μm)	0.38 (0.08-1.77)

* Odds ratio per beat per minute
Abbreviations: CI: confidence interval

Statistical analyses were performed using SPSS software (version 12.0, SPSS Inc, Chicago, Il, USA) and SAS software (The SAS system, release 6.12, Cary, NC, USA: SAS Institute Inc.). A value of $P<0.05$ was considered statistically significant.

Results

Stent analysis; image quality

The 50 patients had a total of 76 stents (1 to 5 stents per patient, average 1.5 ± 0.87) that were studied. A total 41 (54%) and 24 (32%) stents were of respectively good or moderate image quality, whereas stent lumen could not be visualized in the remaining 11 (14%) stents. Reasons of uninterpretability were motion artifacts in 5 (45%) stents and attenuation artefacts in 6 (55%) stents.

Of the uninterpretable stents, 6 were placed in the right coronary artery (RCA), whereas 3 and 2 were positioned in the left anterior descending (LAD) and left circumflex coronary arteries (LCx), respectively. No significant differences were observed in interpretability between the different coronary arteries (P=0.35).

Average heart rate during data acquisition was significantly higher in stents deemed uninterpretable due to motion artifacts (72 ± 9) as compared to stents deemed uninterpretable due to attenuation artefacts (55 ± 2, P=0.002). No significant difference was observed between stents uninterpretable due to attenuation artefacts and interpretable stents (57 ± 9, P=0.62).

In stents positioned without any overlap (n=55), image quality was good in 31 (56%), moderate in 20 (36%) and non-diagnostic in 4 (7%). In contrast, image quality in stents positioned with partial overlap (n=21) was significantly lower as image quality in these stents was good in 10 (48%) and moderate in 4 (19%), whereas 7 (33%) were uninterpretable (P=0.01).

A trend towards improved image quality in stents with thin struts (<140 μm; n=43) could be observed as compared to stents with thick struts (≥140 μm; n=33). In the latter 14 (42%) and 12 (36%) were of respectively good or moderate image quality with 7 (21%) stents being uninterpretable.

In contrast, respectively 27 (63%) and 12 (28%) of stents with thinner struts were of either good or moderate image quality, while 4 (9%) stents were uninterpretable. Still, no statistical significance was observed (P=0.15).

Results from GEE analyses are provided in Table 2.

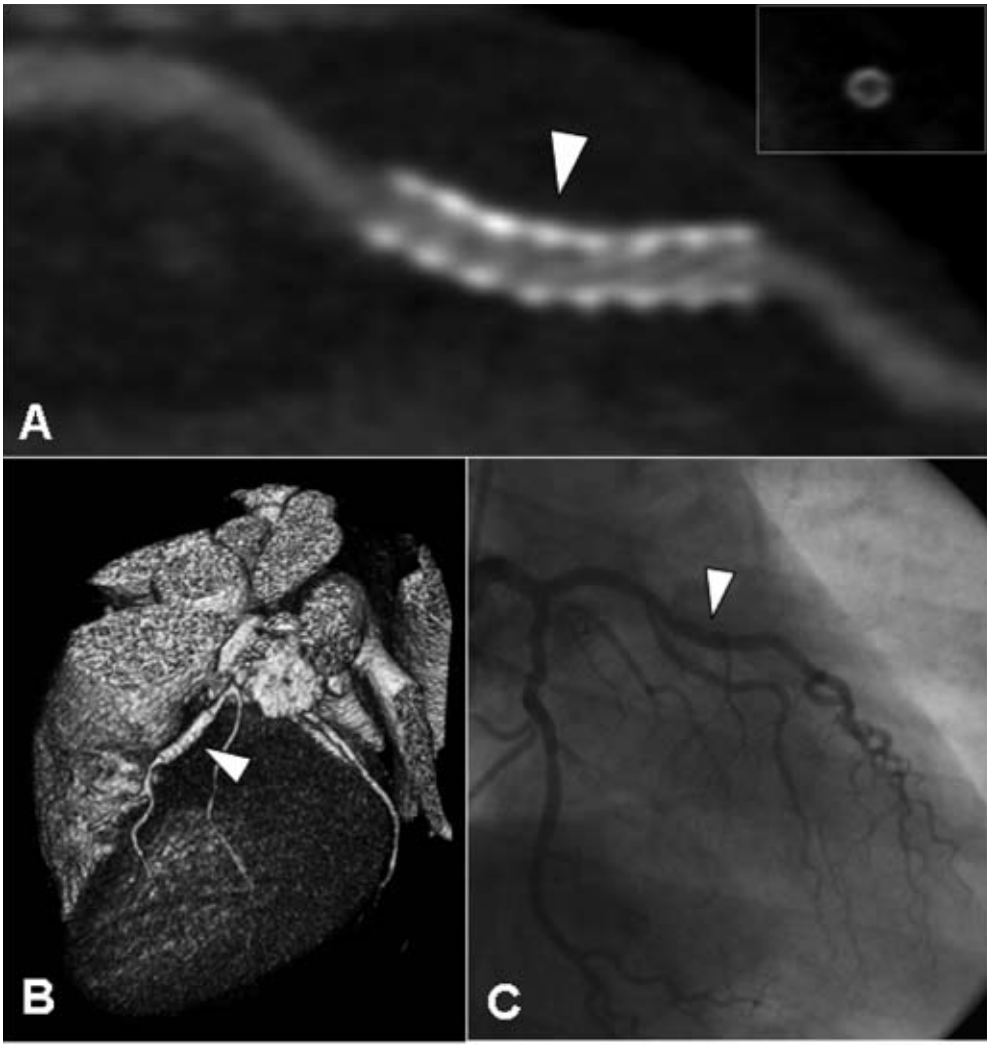

Figure 1. Example of a patent thick-strut drug-eluting stent (diameter 3.5 mm) placed in the left anterior descending coronary artery of a 53-year old male patient. In Panels A and B, a curved multiplanar and 3D volume rendered reconstruction are provided, showing a patent thick-strut drug-eluting stent with only limited neointima hyperplasia (white arrowhead). Also on the cross-sectional image (insert Panel A), no significant in-stent restenosis can be observed. The corresponding conventional coronary angiogram is provided in Panel C.

Stent analysis; diagnosis of (significant) in-stent restenosis (Table 3)

In 7 patients, a total of 21 stents were placed partially overlapping, thereby hampering individual evaluation of the presence of in-stent restenosis. Consequently, overlapping stents were considered as a single stented segment, resulting in the availability of 58 stented segments for the diagnosis of significant (≥50% of lumen diameter reduction) in-stent restenosis. Significant restenosis was correctly ruled out in all 52 stented segments without significant in-stent restenosis as determined by conventional coronary angiography in combination with QCA (Figures 1 and 2). The remaining 6 stented segments with significant in-stent restenosis were correctly identified on MSCT (Figure 3). Accordingly, the sensitivity and specificity for the assessment of significant in-stent restenosis were 100%. In the 52 stented segments without significant in-stent restenosis, average luminal narrowing as determined by QCA was 23.4 ± 8.6% (range: 4.3% to 42.4%). Non-significant restenosis could be observed on MSCT in 37 (71%) stented segments, whereas no neo-intima hyperplasia could be observed on MSCT in 15 stented segments. In stented segments without neo-intima hyperplasia visible on MSCT, average luminal narrowing as determined by QCA was slightly but not significantly lower as compared to that of stented segments with visible neo-intima hyperplasia (20.6% ± 11.7% vs. 24.0% ± 7.6%).

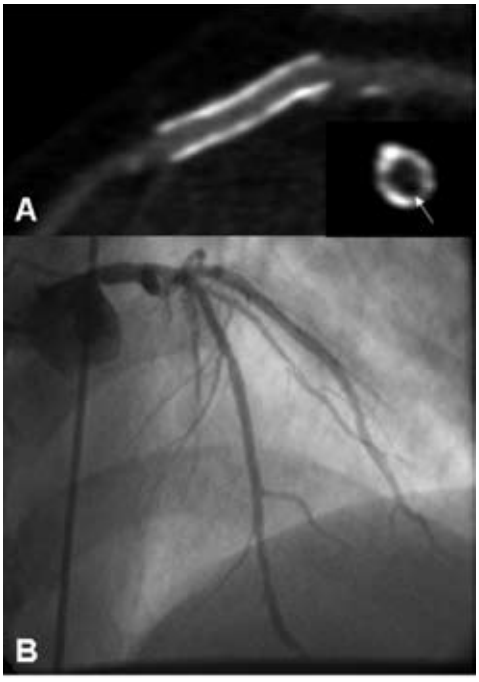

Figure 2. Example of a patent thin-strut, non-drug-eluting stent placed in the left anterior descending coronary artery of a 46-year old male patient. In Panel A, a curved multiplanar reconstruction is provided of a patent thin-strut stent (diameter 3.5 mm). Cross-sectional image perpendicular of the stent (insert) confirms the presence of only minimal in-stent hyperplasia (appearing as a small rim of hypoattenuating tissue, white arrow). Observations were confirmed by invasive coronary angiography (Panel B).

Peri-stent lumina (Table 3)

Of the 76 implanted stents, 21 were positioned (partially) overlapping. As a result, 55 single stented segments and 10 stented segments resulting from overlapping stents were available, including both interpretable as uninterpretable stented segments. Also, 1 stent (located in the RCA) originated directly from the aorta. Accordingly, 64 proximal stent lumina and 65 distal stent lumina were available for analysis. All but 1 (1%) of the 129 peri-stent lumina were of sufficient image quality to evaluate the presence of significant narrowing. Conventional coronary angiography in combination with QCA demonstrated the presence of significant stenosis of 5 peri-stent lumina, which were all correctly identified on MSCT. However, 2 lesions (1 proximal and 1 distal) were overestimated by MSCT, resulting in a specificity of 98%.

Table 3. Diagnostic accuracy to detect (significant) in-stent or peri-stent restenosis.

	≥ 50% in-stent restenosis	Peri-stent restenosis
Assessable*	65/76 (86%, 78% - 94%)	128/129 (99%, 97% - 100%)
Sensitivity	6/6 (100%)	5/5 (100%)
Specificity	52/52 (100%)	121/123 (98%, 96% - 100%)
Positive predictive value	6/6 (100%)	5/7 (71%, 37% - 100)
Negative predictive value	52/52 (100%)	121/121 (100%)

Values are segments (%, 95% confidence intervals).
* Includes all available stents, for the diagnostic accuracy calculations, (partially) overlapping positioned stents were considered as a single stented segment.

Discussion

In our present study, 76 coronary stents were evaluated using 64-slice MSCT, of which 65 (86%) were interpretable. Both elevated heart rate and overlapping positioning appeared to be associated with decreased interpretability, while no effect of stent type or location was observed. In the interpretable stented segments, a sensitivity and specificity to detect significant (≥ 50%) in-stent restenosis of 100% was obtained, whereas the presence of non-obstructing in-stent restenosis was accurately identified in 71% of stented segments. Also the presence of peri-stent stenosis could be accurately detected with a sensitivity and specificity of 100% and 98%, respectively.

Our current observations compare favourably to previous studies reporting on coronary stent imaging with 16-slice MSCT. In an earlier study by Schuijf et al, 21 patients with 65 previously implanted stents were evaluated [9]. A moderate sensitivity 78% and an excellent specificity of 100%, respectively, to detect in-stent restenosis were observed. However, only 50 (77%) of stents proved to be of sufficient image quality for evaluation. Exploration of the characteristics of 23% uninterpretable stents showed that predominantly stents with thicker struts (≥140 μm) as well as stents with smaller diameter (e.g. ≤3.0 mm) tented to suffer from degraded image quality. The effect of thick struts was particularly pronounced, 41% of thick strut stents were uninterpretable, as compared to 11% of stents with thinner struts. Diameter showed less prominent effect, although still a substantially

higher percentage of stents with a diameter ≤3.0 mm was uninterpretable as compared to stents with a larger diameter (28% versus 11%). These observations were recently confirmed in a larger population (143 patients included with a total of 232 stents) [6]. In this study by Gilard et al, also using 16-slice MSCT, a substantial increase in interpretability from 51% to 81% was observed in stents with diameters >3.0 mm as compared to those with diameters ≤3.0 mm. In addition, sensitivity to detect in-stent restenosis increased similarly from 54% to 86%. For all stents, regardless of diameter, a specificity of 100% was observed. In this particular study the effect of strut thickness was not explored.

In our present study, improved interpretability of stents with 64-slice MSCT was observed with sufficient image quality in 86% of stents. Exploration of the characteristics of uninterpretable stents showed that similar to previous studies in native coronary arteries, elevated heart rate was a significant cause of non-diagnostic image quality [18]. Indeed, uninterpretability was due to motion artefacts in 45% of uninterpretable stents. Accordingly, these observations underline the need for adequate heart rate control during MSCT coronary angiography.

Further evaluation of the uninterpretable stents demonstrated that also partially overlapping positioned stents are associated with deteriorated image quality. The increased metal content is likely to amplify high-density artefacts, thereby increasing the artificial narrowing of the stent lumen. Indeed, whereas 93% of single stents were interpretable, 33% of partially overlapping stents were of non-diagnostic quality. Accordingly, in patients with partially overlapping stents, evaluation by means of another modality than MSCT may be preferred. In contrast to previous studies, no pronounced effect of strut thickness was observed. Nonetheless, the presence of thick struts still tended to result in non-diagnostic image quality more often as compared to stents with thin struts (21% versus 9%, P=0.15). Accordingly, the influence of strut thickness on image quality with 64-slice MSCT should be evaluated in larger cohort as our study may have been underpowered to demonstrate any effect.

In the interpretable stented segments, the presence or absence of significant (≥50%) in-stent restenosis was correctly identified in all stented segments. Also, the presence or absence of peri-stent restenosis could be detected with diagnostic accuracy of 98%. In particular, observed negative predictive value to exclude the presence of in-stent or peri-stent restenosis was extremely high. Accordingly, the technique may be well suited for non-invasive rule out of significant (≥50%) in-stent or peri-stent restenosis. Somewhat lower sensitivity and specificity were reported by a recent study employing 40-slice MSCT technology [19]. In this study by Gaspar and colleagues, evaluating 65 patients with 111 implanted coronary stents, a sensitivity and specificity to detect ≥50% in-stent restenosis of 89% and 81% were observed [19]. In part, this discrepancy may be explained by the fact that in this study only a very small number of stents (5%) were excluded from the analysis, whereas the number of excluded stents was higher in our own study. Still, also in the study by Gaspar, a high negative predictive value (97%) was observed, underlining the potential of MSCT as a non-invasive technique to rule out the presence of in-stent restenosis.

Another finding of our study was that in contrast to 16-slice MSCT [9;14] the superior image quality of 64-slice MSCT has improved visualization of non-significant in-stent hyperplasia in addition to significant in-stent restenosis. The presence of in-stent hyperplasia albeit limited was demonstrated

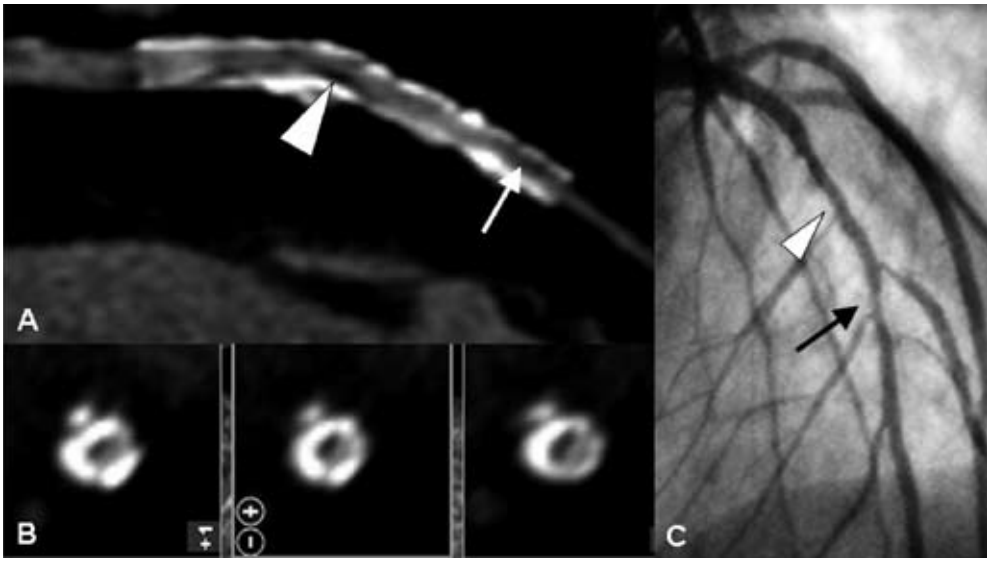

Figure 3. Diagnosis of in-stent restenosis in 2 adjacent stents placed in the left anterior descending coronary artery of a 61-year old male patient. Curved multiplanar reconstruction (Panel A) demonstrates the presence of in-stent restenosis (slightly exceeding 50% luminal diameter narrowing at the mid level [white arrowhead] and more severe at the distal part of the stent [white arrow]) in 2 adjacent non-drug-eluting stents (diameter 3.5 and 3.0 mm). Panel B: Also on the cross-sectional images obtained at the mid level, the presence of in-stent restenosis (appearing as hypoattenuating tissue) can be observed. Panel C: Findings were confirmed by invasive coronary angiography.

by QCA in all stents and correctly recognized in 71% of stents on MSCT as well. Our observations are in line with a recent study by Mahnken et al using 64-slice MSCT in a phantom model [20]. Comparison of16-slice MSCT to 64-slice MSCT in 8 stents with a diameter of 3.0 mm positioned in a static chest phantom showed superior visualization of stent lumina with 64-slice MSCT due to significantly less artificial lumen reduction and image noise. Still, a considerable portion of stent lumina remained obscured even with 64-slice MSCT and in our own study, the presence of neo-intima hyperplasia could not be observed on MSCT in 30% of stents. Accordingly, the value of MSCT to identify moderate in-stent hyperplasia appears to remain limited at present.

Limitations

A relatively small number of patients were evaluated in the present study. As a result, the total number of stents and importantly, the number of patients with significant in-stent restenosis (12%), were relatively low as well. Nonetheless, a much higher prevalence of in-stent restenosis is not likely to be encountered in daily practice and extrapolation of the current results to clinical practice may therefore be justifiable [21;22]. Also, the number of evaluated stents was low and the influence of stent and patient characteristics on stent interpretability should be explored in larger patient cohorts in order

to fully establish which characteristics should potentially be avoided when performing stent evaluation with MSCT. In particular, the range of stent diameters was limited in the present study with an average of 3.4 ± 0.3 mm and as a result a potential effect of stent diameter could not be evaluated in the present study. Thus, our study could possibly best be regarded as a basis for further larger studies concerning image quality and diagnostic accuracy of 64-slice MSCT in coronary stents. In addition, despite the technological advancements of 64-slice MSCT, several limitations inherent to the technique remain. First, as also observed in our present study, a stable and low heart rate remains crucial for high-quality MSCT images and administration of beta-blockers prior to the examination therefore is often required [18]. Finally, an important consideration is the relatively high effective radiation dose (10-15 mSv) to which a patient undergoing MSCT coronary angiography is exposed. For this purpose, dose-modulation protocols are currently under development.

Conclusion

In selected patients with previous stent implantation, sensitivity and specificity of 100% to detect significant (≥50%) in-stent restenosis and 100% and 98%, respectively, to detect significant (≥50%) peri-stent stenosis were observed for 64-slice MSCT. In particular, the technique may be useful for non-invasive exclusion of in-stent or peri-stent restenosis and avoid invasive imaging in a considerable number of patients.

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