Coronary CT angiography with dual source computed tomography in 170 patients
Dekan: Professor Dr. I. B. Authenrieth
1. Berichterstatter: Privatdozent Dr. M. Heuschmid
2. Berichterstatter: Professor Dr. S. Schröder
meinen lieben Eltern
# Table of contents

1. Abstract .......................................................................................................................... 7
2. Introduction ...................................................................................................................... 8
3. Material and methods ..................................................................................................... 9
   3.1 Patients ...................................................................................................................... 9
   3.2 Technical details of examinations ......................................................................... 10
   3.3 Evaluation of examinations ................................................................................ 11
   3.4 Statistical analysis .................................................................................................. 12
4. Results ............................................................................................................................ 13
   4.1 Patients’ characteristics ....................................................................................... 13
   4.2 Calcium score ........................................................................................................ 13
   4.3 Image quality .......................................................................................................... 13
   4.4 Diagnostic accuracy of DSCT .............................................................................. 13
5. Discussion ....................................................................................................................... 17
   5.1 Diagnostic accuracy of DSCT .............................................................................. 17
   5.2 Patients with impaired image quality ................................................................... 17
   5.3 Limitations .............................................................................................................. 18
6. Conclusions ..................................................................................................................... 19
7. Appendix ........................................................................................................................ 20
8. References ...................................................................................................................... 21
Danksagung ...................................................................................................................... 24
Lebenslauf .......................................................................................................................... 25
Coronary CT angiography with dual source computed tomography in 170 patients

Ilias Tsiflikas\textsuperscript{a,}\textsuperscript{*}, Harald Brodoefel\textsuperscript{a}, Anja J. Reimann\textsuperscript{a}, Christoph Thomas\textsuperscript{a}, Dominik Ketelsen\textsuperscript{a}, Stephen Schroeder\textsuperscript{b}, Andreas F. Kopp\textsuperscript{a}, Claus D. Claussen\textsuperscript{a}, Christof Burgstahler\textsuperscript{b}, Martin Heuschmid\textsuperscript{a}

\textsuperscript{a} University Hospital of Tuebingen, Department of Diagnostic and Interventional Radiology, Hoppe-Seyler-Str. 3, 72076 Tuebingen, Germany
\textsuperscript{b} University Hospital of Tuebingen, Department of Cardiology, Hoppe-Seyler-Str. 3, 72076 Tuebingen, Germany

\textsuperscript{*} Corresponding author:
Ilias Tsiflikas
University Hospital of Tuebingen, Department of Diagnostic and Interventional Radiology
Hoppe-Seyler-Str. 3, 72076 Tuebingen, Germany
E-mail address: ilias.tsiflikas@med.uni-tuebingen.de
Introduction: In preliminary studies DSCT provides robust image quality over a wide range of heart rates and excludes CAD with high accuracy. The aim of the present study was to evaluate the reproducibility of these results in a large, unselected and consecutive group of patients scheduled for invasive coronary angiography (ICA).

Material and methods: 170 patients (124 men, 46 women; mean age: 63.6±9.4 years) with known CAD (101 patients) or suspected CAD (69 patients) scheduled for ICA were examined by coronary CTA prior to ICA. All coronary segments were assessed for image quality (1: excellent; 5: non-diagnostic). The presence of significant vessel stenosis (>50%) was calculated using ICA as standard of reference.

Results: A total of 680 vessels were analyzed. Despite 45 arrhythmic patients all analyzed coronary segments were diagnostically evaluable. Mean Agatston score equivalent was 686 (range 0–4950). ICA revealed 364 lesions with ≥50% diameter stenosis. DSCT correctly identified 336 of these lesions. 115 lesions with a diameter stenosis ≤50% were overestimated by DSCT and thus considered as false-positive findings. On a per-segment basis, sensitivity was 92%, specificity 93%, positive predictive value (PPV) was 75% and negative predictive value (NPV) 98%. On a per-vessel basis DSCT revealed a sensitivity of 93%, a specificity of 88%, a PPV of 78% and a NPV of 97%. On a per-patient basis sensitivity was 94%, specificity 79%, PPV 88% and NPV 90%.

Discussion: Initial results of preliminary studies showing robust image quality and high accuracy in DSCT cardiac imaging could be approved with the present study enclosing a large consecutive population. However severe coronary calcifications and irregular heart rate still remain limiting factors for coronary CTA.

Conclusions: Despite improved image quality and high accuracy of coronary DSCT angiography, proof of indication is necessary, due to still remaining limiting factors.
In an aging society, there is an increased prevalence of coronary artery disease (CAD) [1]. Therefore, an early detection of CAD is getting more important. The potential of coronary CT angiography (CTA) with a high negative predictive value to exclude CAD has been shown in several previous studies using multidetector CT (MDCT) [2–8] or dual source CT (DSCT) [9–15]. In preliminary studies the recently introduced DSCT offered an encouraging diagnostic accuracy and it has been shown to provide stable image quality, even for higher heart rates [9–15]. These initial results suggest that this technique might ultimately broaden the indication for CTA and be applied to patients with a higher risk for CAD. Thus, the aim of the present study was to evaluate the reproducibility of the above results in a large, completely unselected and consecutive group of patients scheduled for invasive coronary angiography (ICA).
Material and methods

3.1 Patients

170 consecutive patients (124 men, 46 women; mean age: 63.6 ± 9.4 years) scheduled for invasive coronary angiography were additionally examined with DSCT. Elevated serum creatinine levels >1.5 mg/dl, unstable angina, thyroid disease, pregnancy or allergic reactions to iodinated contrast agents were determined as exclusion criteria. The local Ethics Committee approved the study protocol, and all patients gave informed consent to participate in this study. 120 of 170 patients (71%) were on daily β-blocker medication. Additional β-blocker medication was not administrated. All patients received a double 1.2mg dose isosorbide mononitrate (Nitroglycerin sublingual).

**Table 1. Patients’ characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>age (yrs)</td>
<td>63.6 ± 9.4</td>
</tr>
<tr>
<td>Men / women</td>
<td>124 / 46</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>64 ± 12 (37 – 110)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28 ± 4 (18.8 – 42.9)</td>
</tr>
<tr>
<td>Risk factors</td>
<td>3.5 ± 1.3 (1 – 6)</td>
</tr>
<tr>
<td>Total calcium score(Agatston score equivalent)</td>
<td>686 ± 976 (0 – 4950)</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>274 ± 568 (0 – 2242)</td>
</tr>
<tr>
<td>Left main</td>
<td>36 ± 97 (0 – 748)</td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>305 ± 508 (0 – 3144)</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>112 ± 230 (0 – 1225)</td>
</tr>
<tr>
<td>Total calcium mass (mg CaHA/cm³)</td>
<td>136 ± 198 (0 – 970)</td>
</tr>
</tbody>
</table>

Indication for invasive coronary angiography

<table>
<thead>
<tr>
<th>Indication</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspicion of CAD</td>
<td>69/170 (41%)</td>
</tr>
<tr>
<td>Suspicion of restenosis</td>
<td>101/170 (59%)</td>
</tr>
<tr>
<td>Prevalence of CAD</td>
<td>82%</td>
</tr>
</tbody>
</table>

Variables are presented as mean ± SD (range). Categorical data are presented with absolute frequencies.
3 Material and methods

3.2 Technical details of examinations
All CT examinations were performed using a dual source computed tomography scanner (SOMATOM Definition, Siemens Medical Solutions, Forchheim, Germany). Patients were placed on scanner table in supine position. For detection of total calcium burden, a retrospectively gated non-contrast enhanced scan (1.2mm collimation, 120 kV tube voltage, electrocardiographically modulated tube current with maximum of 200mAeff) was performed before CTA. Circulation time was determined using a test bolus with 20 ml of contrast media (400mg iodine/ml; Imeron 400 Altana, Konstanz, Germany) and a 40 ml saline chaser bolus (flow rate 5 ml/s) with a dual-head injector (CT Stellant; Medrad, Indianola, Pennsylvania). The following scan protocol was used for DSCT angiography: 0.6-mm collimation (cardiac mode), 120-kV tube voltage, 330-ms gantry rotation time and pitch 0.2–0.43 (automatically adapted to the patients’ heart rate). Tube current was 400mA for both tubes with electrocardiographically modulation during different heart cycle phases for dose reduction. According to the patients’ heart rate, the following electrocardiographic pulsing was adopted automatically for maximum tube current within the RR interval: 60–70% (<50 beats/min), 55–70% (51–60 beats/min), 35–70% (61–119 beats/min) and 20–75% (>120 beats/min). The volume of contrast media was adapted to the body weight and the scan duration time (60–70ml) followed by a mixed bolus of the same volume (30% contrast media, 70% saline) and a saline chaser bolus (60 ml). Flow rate was in all patients 5 ml/s. Non-contrast enhanced images were reconstructed using a 3.0-mm effective slice thickness and a 1.5-mm reconstruction increment. The standard reconstruction window was set at 60% of RR interval. For CT angiography images, an effective slice thickness of 0.75-mm and a reconstruction increment of 0.4-mm were chosen. Determination of the reconstruction interval with the fewest motion artifacts was done by reconstructing a slice at the level of the middle of the left ventricle in 5% increments from 0% to 95% of the RR interval. CTA images were reconstructed for diagnostic evaluation to the point with the least motion artifacts of the right and left coronary arteries. Additionally to the original axial slices, multiplanar
3 Material and methods

reconstructions (MPR), sliding thin-slab maximum intensity projection (MIP) and 3-dimensional volume rendered images were reconstructed depending on the individual case.

3.3 Evaluation of examinations

All acquired datasets were evaluated by two experienced observers, who were not aware of the patients’ clinical information or the findings of ICA. Quantitatively evaluation of total coronary calcium burden was performed with a standard built-in algorithm on an offline workstation (Syngo Multimodality Workplace Siemens, Siemens, Erlangen, Germany). Agatston score equivalent (ASE) as well as total calcium mass in milligramms/cm3 of calciumhydroxyapatite were measured.

Image quality was approximately assessed with regard to the diagnostic evaluation of the left and the right coronary artery and was graded as follows: 1, excellent; 2, good; 3, diagnostic; 4a, diagnostically limited due to severe calcification; 4b, diagnostically limited due to motion artifacts; 5, non-diagnostic image quality.

Furthermore quantitative evaluation of vessel stenosis was performed and all lesions ≥50% were included in the analysis. Using a modified classification of the American Heart Association excluding the two most distal segments of left circumflex artery (segments 14 and 15), all coronary segments were documented separately [16]. In this model the most distal segments of left circumflex artery were excluded, because of their variety and small diameter.

ICA was performed within 1 day after DSCT. All angiograms were evaluated by an independent, experienced interventional cardiologist unaware of DSCT results using quantitative coronary analysis with automated vessel contour detection (Quantitative Coronary Analysis, Philips, Best, The Netherlands). Lesions with a diameter ≥50% were considered significant. All coronary vessel segments were included in statistical analysis. ICA was regarded as standard of reference in detecting relevant vascular stenosis.
3.4 Statistical analysis

In comparison with ICA DSCT results were analyzed on a segmental basis, per coronary artery and per patient. In case of detecting more than one lesion per segment, the most severe lesion determined the diagnostic accuracy of the assessment.

Categorical data were presented with absolute frequencies and percentages. Continuous variables are shown as means ± SDs.
4.1 Patients’ characteristics
The patients’ characteristics are listed in Table 1. DSCT and ICA were performed in all 170 patients without problems. In 101 of 170 patients, there was a known CAD and they were scheduled for ICA because of suspected restenosis. Prevalence for CAD was 82%. Mean heart rate during the scan was $64 \pm 12$ beats/min. 45 of 170 patients (26%) were not in sinus rhythm during the scan.

4.2 Calcium score
The mean calcium score (in Agatston score equivalent) was $686 \pm 976$ (median 236, range 0 – 4950) and the mean calcium mass was $136 \pm 198$mg CaHA/cm$^3$ (median 44, range 0 – 970) (Table 1).

4.3 Image quality
Image quality was analyzed for a total of 2210 segments; hereof 121 segments with stents were not diagnostically assessed and excluded from the analyses. Out of the remaining 2089 segments, 1837 (88%) proved to have good or acceptable image quality whereas 252 segments (12%) were of limited image quality but no segment was rated not diagnostic. In detail, image quality was graded as excellent in 444 segments (21.2%) and as good in 988 segments (47.3%). 405 segments (19.4%) were considered to have diagnostic image quality. Severe calcifications had an impact on image quality of 164 segments (7.9%). Furthermore image quality of 88 segments (4.2%) was affected by motion artifacts.

4.4 Diagnostic accuracy of DSCT
A total of 364 lesions with $\geq 50\%$ diameter stenosis were detected with ICA. 336 of these lesions were correctly identified with DSCT (Fig. 1). Due to insufficient image quality caused by calcifications and/or motion artifacts, 28 of the 364
4 Results

lesions were not correctly assessed with DSCT. Furthermore 115 lesions with a luminal narrowing ≤50% according to ICA were overestimated with DSCT (Table 2).

![Fig. 1](image1.png)

Fig. 1. 73-year-old man with suspected CAD (risk factors: smoking, hyperlipidemia, diabetes mellitus II, body mass index 34 kg/m²). Mean heart rate during examination 74 beats/min. Calcium scoring revealed an Agatston Score equivalent of 560. Coronary DSCT angiography depicted a relevant stenosis of the right coronary artery (A: maximum intensity projection) which could be affirmed with ICA (B). Furthermore there could be shown a relevant stenosis of the LAD (C: curved MIP, D: ICA).

On a per-segment basis, sensitivity was 92%, specificity 93%, positive predictive value (PPV) was 75% and negative predictive value (NPV) 98%.
4 Results

A total of 680 vessels were analyzed. On a per-vessel basis DSCT revealed a sensitivity of 93%, a specificity of 88%, a PPV of 78% and a NPV of 97%. DSCT correctly detected significant CAD in 98 of 104 patients. In 6 patients a significant stenosis was not diagnosed, hereof 4 missed stenosis were located in the distal segment of the left circumflex artery and 2 in the second diagonal branch.

On a per-patient basis sensitivity was 94%, specificity 79%, PPV 88% and NPV 90%.

NPV showed a minor variation with values between 99% for excellent image quality and 96% for image quality limited by motion artifacts. In the same subgroup, specificity decreased from 99% to 67% (Chart 1).

Table 2. Diagnostic accuracy of dual-source computed tomography (DSCT)

<table>
<thead>
<tr>
<th>Diagnostic accuracy of DSCT</th>
<th>RCA</th>
<th>LM</th>
<th>LAD</th>
<th>LCX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary artery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesions &gt;50% in ICA</td>
<td>120</td>
<td>10</td>
<td>169</td>
<td>97</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>100</td>
<td>100</td>
<td>93</td>
<td>82</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>94</td>
<td>95</td>
<td>93</td>
<td>93</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>78</td>
<td>56</td>
<td>73</td>
<td>72</td>
</tr>
<tr>
<td>NPV (%)</td>
<td>100</td>
<td>100</td>
<td>99</td>
<td>96</td>
</tr>
<tr>
<td>True positive</td>
<td>111</td>
<td>10</td>
<td>149</td>
<td>76</td>
</tr>
<tr>
<td>False positive</td>
<td>32</td>
<td>8</td>
<td>54</td>
<td>29</td>
</tr>
<tr>
<td>True negative</td>
<td>500</td>
<td>152</td>
<td>742</td>
<td>368</td>
</tr>
<tr>
<td>False negative</td>
<td>0</td>
<td>0</td>
<td>11</td>
<td>17</td>
</tr>
</tbody>
</table>
4 Results

Chart 1. Diagnostic accuracy of DSCT according to image quality
5.1 Diagnostic accuracy of DSCT
The challenge for early four- and sixteen-slice MDCT have been the small diameter of the coronary segments and their rapid movement throughout the coronary cycle. Consequently, the main cause of low image quality and the restricted diagnostic accuracy have been residual motion artifacts [17–19]. With an increased temporal and spatial resolution 64-detector row CT proved in several studies an acceptable image quality and a high diagnostic accuracy despite of still remaining limitations like higher heart rates [5, 7, 20, 21]. In the present study we were able to reproduce the distinguished results of preliminary studies for the new dual-source computed tomography [10, 12–14, 22] in an unselected, consecutive patient collective with a high prevalence of coronary artery disease (83%). Our results with a NPV of 98% on a per-segment-basis do not essentially differ from the results of prior studies and the PPV of 75% is even lower than the results with 64-slice MDCT. But when considering the unselected patient collective with high prevalence of CAD and arrhythmic heart rate our results confirm a further stabilized image quality of DSCT leading to a high diagnostic accuracy in excluding CAD.

5.2 Patients with impaired image quality
Despite the high prevalence of CAD and the high number of patients not in sinus rhythm (45 of 170; 26%), all examinations in our study were diagnostically evaluable. Even in patients with impaired image quality this study provides an acceptable NPV of 96%. In previous studies with prior CT scanners, there was an impaired image quality with less evaluable coronary segments in patients with arrhythmia and high prevalence of CAD [23–25]. As shown by the relatively low PPV in our study, coronary stenosis may still be overestimated in CTA. The low PPV is caused by the high prevalence for
coronary plaques and indicates that severe calcifications are still a limiting factor for CTA.
Yet, in these cases invasive angiography may then be performed with a solid indication and the option to treat significant lesions. Furthermore it is important to mention that an exact comparison of accuracy between 64-slice MDCT and DSCT is difficult because of the different study populations [5, 20]. Altogether, increased temporal resolution of DSCT of 83ms leads to stabilized image quality and therefore to a higher accuracy in examination of patients with advanced CAD or even of patients with higher irregular heart rates.

DSCT seems to be a powerful tool for excluding CAD in the clinical workup for patients with mentioned CAD. In addition to information on vessel patency, coronary CTA offers the assessment of the vessel wall, the cardiac valves as well as cardiac function [26–29]. Likewise there are often some incidental extracardial findings in the scan field such as pulmonary nodules, pulmonary embolism or hiatal hernia [30].

5.3 Limitations
There are some limitations to the present study that need to be mentioned. A potential limitation of this study is the unselected, consecutive patient group scheduled for ICA anyway with an overall higher incidence for CAD. In these patients the clinical value of CT is limited. In fact, according to current recommendations, the acceptable indication for coronary CTA is excluding CAD in patients with low to intermediate pretest probability. For such a patient group results may differ, e.g. with a higher specificity and/or lower sensitivity. Furthermore stented segments were excluded from evaluation because they are still a challenge for CTA. Segments 14 and 15 were excluded from our analysis, thus potentially making comparison to other studies more difficult.
6 Conclusions

Coronary DSCT angiography proved to have a robust image quality and provide a high accuracy in excluding CAD even in an unselected consecutive group of patients with a higher prevalence for CAD. Therefore results of preliminary studies as well as potency of coronary DSCT angiography as a non-invasive tool in cardiac imaging could be confirmed.
7 Appendix

7.1 Figures and Tables
Table 1: Patients’ characteristics ................................................................. 9
Fig.1: Case presentation: CT and ICA images .............................................. 14
Table 2: Diagnostic accuracy of dual-source computed tomography (DSCT) ... 15
Chart 1: Diagnostic accuracy of DSCT according to image quality ............... 16

7.2 Abbreviations
MDCT: Multi-detector computed tomography
DSCT: Dual-source computed tomography
ICA: Invasive coronary angiography
CTA: Computed tomography angiography
MPR: Multiplanar reconstruction
MIP: Maximum intensity projection
ASE: Agatston score equivalent
CaHA: Calcium hydroxyapatite
RCA: Right coronary artery
LM: Left main coronary artery
LAD: Left anterior descending coronary artery
LCX: Left circumflex coronary artery
SD: Standard deviation
PPV: Positive predictive value
NPV: Negative predictive value
8 References


8 References


8 References

Danksagung

An dieser Stelle möchte ich mich bei allen Personen bedanken, die zum gelingen dieser Arbeit beigetragen haben.

Herrn PD Dr. Martin Heuschmid danke ich für die Überlassung des Themas und der wissenschaftlichen Betreuung. Ebenso wichtig und die Grundlage für das Zustande kommen dieser Dissertation ist die Möglichkeit in der Abteilung für Diagnostische und Interventionelle Radiologie von Herrn Prof. Dr. Claus D. Claussen tätig zu sein, wofür ich ihm und Herrn Prof. Andreas Kopp sehr dankbar bin.

Des Weiteren möchte ich mich bei allen Kollegen, die mir mit Rat und Tat zur Seite standen bedanken, vor allem hervorzuheben wären hier Herr PD Dr. Christof Burgstahler, Frau Dr. Anja Reimann und Herr Dr. Harald Brodoefel.

Für die langen Stunden vor dem CT-Scanner und die vielen wertvollen praktischen Tipps möchte ich Frau Ayser Birinci-Aydogan danken.

Und natürlich gebührt ein ganz besonderer Dank meinen Eltern, die mir mein Studium ermöglicht haben und ohne die ich nicht an diesem Punkt stehen würde.

Auch möchte ich meinen Geschwistern, Freunden und allen anderen Menschen, die mich durch mein Leben begleiten und immer für mich da sind danken.
Lebenslauf

Persönliche Daten

Name    Ilias Tsiflikas
Geburtsdatum  01.01.1980
Geburtsort    Esslingen am Neckar
Familienstand ledig

Schulausbildung

1986 – 1990 Grundschule Reichenbach
1990 – 1999 Gymnasium Plochingen
  • Abschluss: Allgemeine Hochschulreife

Hochschulausbildung

05/2000 - 05/2006 Studium der Humanmedizin
  an der Eberhard-Karls-Universität Tübingen
  • April 2002 Ärztliche Vorprüfung
  • April 2003 Erster Abschnitt der Ärztlichen Prüfung
  • April 2005 Zweiter Abschnitt der Ärztlichen Prüfung
  • Mai 2006 Dritter Abschnitt der Ärztlichen Prüfung

Praktisches Jahr

  Universitätshospital Alexandroupolis, Griechenland
  Paracelsus-Krankenhaus Ruit
  Paracelsus-Krankenhaus Ruit

Beruflicher Werdegang

seit 01.08.2006 Assistenzarzt in der Abteilung für Diagnostische
  und Interventionelle Radiologie des Universitätsklinikums
  Tübingen