**The influence of adaptive iterative dose reduction 3D and temporal averaging on contour sharpness of dynamic myocardial CT perfusion**

*Feger S.¹, Shaban A.¹, Bokelmann B.¹, Kendziorra C., Lukas S.¹, Zimmermann E.¹, Rief M.¹, Dewey M.¹*

¹Department of Radiology; Charité Universitätsmedizin Berlin; Berlin Charitéplatz 1, 10117 Berlin

**Abstract**

**Purpose**

Myocardial computed tomography perfusion (CTP) analysis allows the assessment of the functional relevance of a coronary stenosis. Dynamic CTP may be used to quantitatively analyze the absolute myocardial blood flow, but image quality is limited due to motion artefacts. Temporal averaging and iterative reconstructions were introduced to improve image quality. However, they are supposed to deteriorate image sharpness. Thus, the aim of this study was to investigate the influence of temporal averaging and adaptive iterative dose reduction 3D (AIDR 3D) on the contour sharpness of dynamic myocardial CTP analysis.

**Method and Materials**

The dynamic myocardial CTP datasets of 29 patients acquired at 9.5±2.0 mSv were reconstructed with filtered back projection (FBP) and strong levels of AIDR 3D. Temporal averaging without motion correction was performed as postprocessing step by combining two, three, four, six, and eight original 3D datasets. We compared the contour sharpness based on two different parameters including 4 edges of the myocardium: the distance between the 25% and 75% value between the minimal and maximal grey values (d) and the slope between the 25% and 75% points (m).

**Results**

Both objective contour sharpness parameters showed the tendency to be deteriorated for strong levels of AIDR 3D compared with FBP (d=2.50 mm versus 2.27 mm; m=121.31 HU/mm versus 145.24 HU/mm summarized for all 4 edges; for d p=0.02 at edge 1, p n.s.at edges 2-4 and for m p<0.04 for all edges, respectively). With increasing levels of temporal averaging contour sharpness was slightly deteriorated. Best values for contour sharpness were acquired without temporal averaging (d=2.08 mm, m=167.34). Contour sharpness was worst for strongest levels of temporal averaging (d=2.52 mm, m=117.68; comparison between lowest and highest temporal averaging level: for d p>0.17 at all edges and for m p<0.019 at edges 1,3,4 and p n.s. at edge 2).

**Conclusion**

The usage of higher levels of temporal averaging without motion correction and with strong levels of AIDR 3D slightly deteriorated objective contour sharpness parameters of dynamic myocardial CTP.

**Abbreviations**

computed tomography angiography CTA

conventional coronary angiography CCA

single photon emission CT myocardial perfusion imaging SPECT-MPI

stress magnetic resonance imaging MRI

signal- to- noise ratio SNR

contrast- to- noise ratio CNR

coronary artery disease CAD

field of view FOV

filtered back projection FBP

Adaptive Iterative Dose Reduction 3D AIDR 3D

left ventricle LV

distance between 25% and 75% value between the minimal and maximal grey value d

slope between 25% and 75% value points m

multiplanar reconstruction MPR

**Introduction**

While non-invasive CT coronary angiography (CTA) is highly accurate in diagnosing coronary artery stenoses [1, 2] as compared with conventional coronary angiography (CCA), there are limitations in the assessment of the hemodynamic relevance of coronary stenosis [3]. This is especially relevant in patients with intermediate coronary stenosis of 30-70% [3], in the case of heavily calcified plaques or if coronary stents are present [4] that might reduce the evaluability of the corresponding coronary segment due to artefacts resulting from the stent strut.

Thus, myocardial CT perfusion is a promising approach to detect myocardial ischemia as a predictor of the functional relevance of a coronary stenosis diagnosed during CTA [5, 6]. Compared with single photon emission CT myocardial perfusion imaging (SPECT-MPI) or stress magnetic resonance imaging (MRI) which are commonly used diagnostic tests in clinical routine, CTP shows a very high diagnostic accuracy [7-9]. A relevant advantage of myocardial CTP is the possibility to perform anatomic and functional assessment (CTA and CTP) in a single session [10], which further improves the diagnostic correctness as compared with CTP alone [11, 12]. In general, CTP can be performed as static myocardial CTP with data acquisition at one single time point [13] or as dynamic 4 dimensional myocardial CTP (4D CTP) [14]. By enabling the image acquisition at different points of time, this approach allows the quantitative analysis of the absolute myocardial blood flow. Additionally, time attenuation curves can be ascertained during the first pass, the arterial phase and the microcirculation phase [15]. Only dynamic 4D CTP allows the determination of absolute perfusion parameters by analysing the input and output function of the myocardial blood flow [16].

Despite the huge potential of dynamic 4D CTP there are important challenges due to the acquisition at several time points that have to be addressed. The radiation exposure is potentially high due to multiple acquisitions [15]. The reduction of scan parameters in order to reduce high radiation exposure results in image noise and motion artefacts. To address these challenges temporal averaging of multiple datasets or iterative reconstructions can be applied to improve image quality. However, these approaches are supposed to deteriorate image sharpness due to their edges-smoothing design. At the current status, there are two feasibility studies on temporal averaging [17]. However, this is the first study addressing the influence of temporal averaging and iterative reconstruction on the contour sharpness of dynamic myocardial 4D CTP.

**Methods**

**Study design**

This is the image quality substudy of the prospective 4D CT perfusion pilot study [18]. The detailed description of in- and exclusion criteria, patient preparation and CT protocol are already publishes within the main study. Altogether, we included 29 of the 34 patients who underwent both, cardiac CTA and dynamic myocardial 4D CTP on a 320-row CT scanner (Aquilion ONE, Toshiba Medical Systems, Otawara, Japan). 4D CTP was performed after adenosine administration and patients received contrast agent for both the CTA and CTP. All patients were referred to and had clinical indications for cardiac CT. We included at least 40 year-old patients with suspected or known coronary artery disease (CAD). In the following cases the patients were not eligible: any coronary intervention during the last three months, after coronary artery bypass grafting, creatinine >2.0 mg/dl, no sinus rhythm, heart failure (NYHA III or IV), moderate to severe aortic stenosis, severe chronic obstructive lung disease, pregnancy, sildenafil intake in the last 48 hours, chronic therapy with dipyridamol, inability to hold the breath for 15 s, preexisting severe hypotension, atrioventricular block of grade two and three, sick sinus syndrome, unstable angina pectoris. Our Institutional Review Board approved this prospective pilot study and all patients provided written informed consent.

**Patient preparation**

In order to reduce the heart rate and variability, patients with a heart rate of >60 bpm received beta blockers before the CT examination (n=14 only oral betablockers [atenolol, Tenormin 50, Astra-Zeneca], and n=6 oral and and i.v. beta blockade [esmolol, Brevibloc, Baxter]). Further three patients were administered 5 (1 patient) or 10 mg (2 patients) of ivabradin (Procoralan, Servier). Immediately before the CT scan all patients received sublingual nitroglycerine (1.2 mg). The patients were informed in advance about not to take any xanthine-containing food and beverages at least twelve hours before adenosine injection. The administration of xanthine-containing medicine (theophylline) was avoided 24 hours before the adenosine injection, due to possible antagonistic effects of xanthine, which could decrease the effect of adenosine.

**Coronary CTA and dynamic myocardial 4D CTP**

Calcium scoring (CACS) was performed without injection of contrast agent at 100kV and 140mA, covering 14cm of the heart in z-direction.

The CTA was planned based on the position of the coronary arteries on CACS plus 15 mm in each direction of the z-axis. Tube voltage was 120 kV for patients with BMI < 36 und 135 kV for BMI ≥ 36. See the main manuscript for further details. For both, the CTA and CTP, the patients received nonionic contrast agent (Iobitridol, 350 mg of iodine per milliliter, Xentix 350, Guerbet, France) through in intravenous line with a flow of 7 ml/s in the right antecubital vein. For CTA and CTP, the patients were administered 58 ml and 42 ml of contrast agent, respectively, followed by a saline flush of 80 ml. CTP always followed the CTA, and was initiated after continuous infusion of adenosine for 3 min.

Coverage in z-direction for CTP was that of the myocardium from CACS plus 10 mm in each direction in order to not miss parts of the myocardium during dynamic CTP, or plus 15 mm in the case of a high position deviation in z direction between CACS before CTA and CTP. The arterial input function of the CTA sure start was used to determine the CTP start point after contrast agent injection. In each case, scanning was performed from 70-80% of the RR interval. The dynamic 4D CTP with one acquisition every heart beat was followed by three single late phases 10, 20 and 35 s after the dynamic scan, respectively. In order to cover 20 heart beats, the total scan time of the dynamic phase was adjusted to the individual heart rate. CTP was initiated after continuous infusion of adenosine for 3 min. Image acquisition was performed with a gantry rotation time of 350 ms, tube voltage of 100 kV and tube current of 140 mA for patients with BMI ≤ 30 and 200 mA for BMI > 30. The vasodilatory effective adenosine was adapted to the body weight (140 μg/kg/min) and administered over a maximum of six minutes continuously, with an intravenous infusion through the left cubital vein using a perfusion system.

**Image evaluation**

CT image reconstruction

We performed the CT image reconstruction by using an imaging matrix of 512 x 512 pixels covering a field of view (FOV) of 180 mm in axial direction. The reconstructions were performed in 5% intervals of the available RR interval in all patients, and additionally of the visually chosen best phase. We performed reconstructions with filtered back projection (FBP) and strong levels of the Adaptive Iterative Dose Reduction 3D (AIDR-3D) [11] algorithm, as they have been shown to demonstrate higher objective image quality parameters compared to mild and standard levels [19].

Temporal averaging

Temporal averaging of several consecutive 3D datasets was used in order to improve image quality and to reduce motion artefacts. Therefore, we combined one, two, three, four, six, and eight original 3D datasets from consecutive heart beats and temporal averaging into one new 3D dataset to test the different levels. Thus, six 4D reconstructions with the different levels of temporal averaging were generated in all 29 patients that resulted in altogether 174 4D CTP datasets. The averaged images were calculated as the arithmetic mean of the input images. The value of an output voxel followed the formula

,

where I is a voxel value, N the number of combinations, X the voxel position, and t the time. This process was performed before reading as postprocessing step. See the main manuscript for further details.

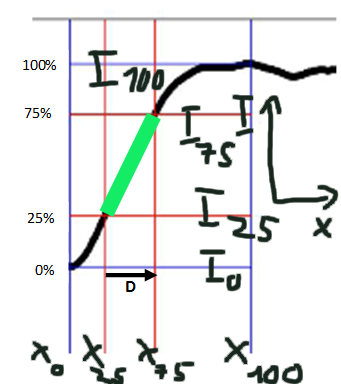
Contour sharpness analysis

All 174 dynamic 4D CTP datasets were analysed with the software framework CardiacPerfusion (<https://github.com/CardiacImagingCharite/CardiacPerfusion>). For the analysis of the contour sharpness, a straight line was placed above the heart displayed as 4-chamber view connecting the myocardium of the left and the right ventricle, thereby carefully avoiding the integration of any perfusion defects or blooming artefacts into the measurement. Thus, we integrated 4 different edges of the myocardium being localised between: 1) the right ventricle and the septal myocardium, 2) the septal myocardium and left ventricle, 3) the left ventricle and lateral left ventricular myocardium and 4) the lateral left ventricular myocardium and surrounding epicardial tissue.

We used two different parameters to objectively evaluate the contour sharpness: the distance between the 25% and 75% betwenn the minimal and maximal grey value of each reconstruction to exclude outliers from the analysis and the slope as further contour sharpness parameter, that was defined as the distance between 25% and 75% between the maximal and minimal grey value in the contour divided by the distance calculated before. In case of multiple appearance of the 25% or 75% values, that may occur for non bijective curves, always the outermost points were chosen for calculation.

**d = | x75 – x25|**

**m = | I75 – I25| /** d



Hence, a sharp contour would be characterized by a small distance between 25% and 75% values between the minimal and maximal grey value (first parameter) and high value of the slope at this distance in the contour (second parameter).

**Statistical Analysis**

Values are given as arithmetic mean (standard deviation) if not mentioned otherwise. We performed the statistical analysis by using SPSS version 20. First, we used Shapiro-Wilk test to check normal distribution. If the values were normally distributed, we used ANOVA as overall test for repeated measurements for the comparison between the different temporal averaging levels, and *t*-test for dependent values was used for the respective single comparisons. If normal distribution was refused, we used Friedman test as overall test and Wilcoxon signed-rank test for the single comparisons. Since we included only two different reconstructions into this analyses (FBP and AIDR 3D) overall testing was not necessary for the comparison between the reconstructions. The p value for the single tests was adapted to <0.003 indicating statistical significance according to Bonferroni corrections for the fifteen possible comparisons between the five temporal averaging levels: 0-1, 0-2, 0-3, 0-5, 0-7, 1-2, 1-3, 1-5, 1-7, 2-3, 2-5, 2-7, 3-5, 3-7, 5-7. For the comparison between the two reconstructions a p value of <0.05 was considered as statistically significant.

**Results**

**Patient characteristics**

The 30 included patients had a mean age of 64 years and showed a male-to-female ratio of 9:1 (Table 1). More than 80% of the patients had any type of chest pain with approximately one third suffering from typical angina pectoris. Almost two third of the patients had known CAD with prior myocardial infarction. All examinations were successfully performed and all temporal average reconstructions could be generated resulting in 174 4D CTP datasets.

**Contour sharpness**

**AIDR 3D versus FBP**

Contour sharpness parameters were slightly deteriorated for AIDR 3D strong versus FBP at all 4 edges of the myocardium, as demonstrated by reduced values for the distance between 25% and 75% grey values, but higher values for the slope (Figure 1).

In detail, the comparison of the slope showed higher values for FBP than for strong levels of AIDR 3D (FBP 145.2±127.2 HU/mm versus AIDR 3D 121.3±101.8 HU/mm, p<0.023, respectively; Table 2). The distance between the 25% and 75% grey value showed the tendency to be higher for AIDR 3D strong as compared with FBP, but without statistical significe (FBP 2.3±1.5 mm versus AIDR 3D 2.5±1.4 mm, p>0.059, respectively; Table 2). This is also demonstrated by the visual impression of a “smooth edge”, being characterised by reduced variation of Hounsfield Units (HU) within one contour of a single edge, as shown in Figure 2.

**Different additions**

Higher levels of temporal averaging showed slightly deteriorated values for both contour sharpness parameters, in detail that means lower values for the distance between the 25% and 75% grey values and increased values for theslope (Figure 1).

Thus, with increasing levels of temporal averaging the slope was deteriorated at all 4 edges (p<0.01 at all 4 edges; m for maximal temporal averaging 117.7±102.4 versus 167.3±150.0 without temporal averaging, see Table 3 for further results). The distance between 25% and 75% grey values showed the same tendency, but was without statistical significance (p>0.052 at all 4 edges). Best values were achieved without temporal averaging, the maximal temporal averaging levels showed the lowest values (d was 2.1±1.3 mm without temporal averaging versus 2.5±1.4 mm with maximal addition level), indicating the strongest reduction of contour sharpness. This goes in line with the visual impression of a “smooth edge” with reduced variation of HU within one contour of a single edge with increasing levels of temporal averaging (Figure 2).

**Discussion**

The application of AIDR 3D and temporal averaging is a promising approach to improve the image quality of 4D dynamic CTP of the entire myocardium, but is characterized by a slight deterioration of contour sharpness. In our analysis both objective contour sharpness parameters were slightly deteriorated for strong levels of AIDR 3D compared with FBP, and for increasing levels of temporal averaging. Contour sharpness analysis in this study is based on two different but complementary parameters, thereby following established approaches [20]. These quantitative image quality parameters were measured at all relevant anatomical locations for myocardial CT perfusion imaging, thereby including all available edges of the left ventricular myocardium. Since deteriorated contour sharpness is expected to reduce the evaluability due to blurring of the structures, contour sharpness is supposed to be a very valuable quantitative parameter for image quality analysis.

Currently, only limited data is available to prove feasibility of 4D dynamic CTP of the entire myocardium. There is one study with 32 Asian patients [17], showing a good correlation of the myocardial blood flow and coronary flow reserve of 4D dynamic CTP compared with positron-emission tomography. In addition, the main results of this study published within the main manuscript considered further objective (noise, SNR and CNR) and subjective image quality parameters [18]. For 4D dynamic CTP, multiple 3D datasets are acquired, in this study at least 20 heart beats per patient. While we scanned at relatively low dose for each single acquisition compared with the acquisition for CTA (Dosis-Werte), due to the multiple acquisitions the summed radiation dose is higher compared with a single shoot for CTA (Dosis). However, scanning at multiple time points ensures that the optimal time point to demark a perfusion defect cannot be missed. Despite this advantages, bridging the gap between low radiation dose and optimal image quality is a huge challenge for 4D dynamic CTP of the myocardium. Different approaches exist and have been applied in this analysis to optimize image quality without requiring the adjustment of scanning parameters which would result in increasing the radiation exposure: strong levels of AIDR 3D and temporal averaging of consecutive heart beats.

The AIDR 3D algorithm uses a scanner and a statistical noise model in combination with a projection noise estimation in the raw data domain enabling the reduction of photon and electric noise. Subsequently, the initial reference image is produced and incorporated into the iteration cycle which is model-based and considers the anatomical region, including contours and edges, and the reconstruction kernel. After each iteration, the output image is being compared with the reference image with special regards to the contour which can be reconstructed from the initial FBP image (so called blending). Thus, this approach is expected not to relevantly deteriorating the imaging sharpness, since contour details are supposed to be considered for the final image. In our analysis, contour sharpness was slightly reduced, suggesting that the AIDR 3D algorithm imperfectly reconstructs the edges from the FBP image. Nevertheless, this effect was not strongly pronounced. A recent study of Feger et al. [19] analysed the influence of AIDR 3D levels on contour sharpness parameters of coronary arteries for CTA and did not find a relevant difference between AIDR 3D and FBP. This could be due to the different characteristics of coronary arteries and the myocardium, such as the smoothness of the surfaces, as well as the contrast of the object of interest and the adjacent volume. During CTA, the coronary arteries are very well contrasted, resulting in relatively sharp edges in general, whereas the myocardium for CTP is in general less contrasted. Another important difference are the used scanning parameters. Since dynamic 4D myocardial CTP is acquired at multiple points of time, scanning parameters for a single acquisition are reduced to meet the radiation exposure requirements for scanning real patients, resulting in higher image noise of the FBP image compared with the CTA acquisition. This could have an effect on the contour sharpness for the FBP image, as well as the contour sharpness differs if iterative reconstructions are applied.

In addition, we used temporal averaging by combining and overlapping different 3D CTP datasets acquired during consecutive heartbeats. The adjustment of the number of 3D datasets being incorporated for the resulting image results in different temporal averaging levels. Since the overlapped images are acquired at different time points, the resulting 3D dataset is supposed to more markedly display perfusion abnormalities compared with the single images, since the optimal point of time for detecting the deficit would always be displayed. In general, the optimal time point which best demonstrates a perfusion deficit can only hardly be foreseen and thus, when analysing single acquisition images, the optimalpoint of time can easily be missed. However, temporal averaging is supposed to reduce contour sharpness due to the overlap of multiple 3D datasets and the motion of objects in between. This was demonstrated in our study as well: With higher levels of temporal averaging contour sharpness parameters were slightly reduced. In addition, in this study no motion correction approaches have been applied. Thus, even if scanning conditions are being optimized (no motion due to the patients’ breathing or body motion during the scan), motion of the heart cannot be fully prevented. As a consequence, it is obvious that with increasing temporal averaging levels the contours will be blurred, resulting in reduced contour sharpness parameters.

The influence of temporal averaging on further objectives (including signal, noise, SNR and CNR) and subjective image quality parameters (subjective quality, motion and evaluability of perfusion defects) was already analysed within the main study, and they were most advantageous for medium temporal averaging levels (averaging of 3 consecutive 3D datasets). Image quality parameters were worse for stronger temporal averaging levels covering more than 3 3D datasets, especially with regards to the CNR values. In the clinical context, the results of the main study and this substudy are complementary and need to be seen as a whole. While contour sharpness was reduced with increasing levels of temporal averaging, best performance with regards to objective and subjective image quality parameters was achieved with medium levels of temporal averaging. Probably, the effect of reduced contour sharpness is too little pronounced for deteriorating the overall image quality and evaluability of medium temporal averaging levels.

Limitations of this manuscript include the small sample size of only 29 patients. In this work, we did not use motion correction, which would improve the contour sharpness especially for higher levels of temporal averaging. Even though we minimized motion of the patients during image acquisition with a very careful patient preparation, it is not possible to completely avoid the motion of the patients` heart. It would have been interesting to compare temporally averaged datasets, which are motion corrected with regards to their influence of the contour sharpness that is supposed to be improved compared with non-motion corrected images. In addition, in this analysis we only used one objective parameter, which cannot cover all aspects of image quality. Therefore, we evaluated the results of this work in the context of the results of the main manuscript to cover multiple objective and subjective aspects. Our scanning parameters were relatively low at 100 kV and 150 mA, which as a reasonable approach in clinical practice, since the aim in real patients is to reduce the radiation exposure to values as low as possible. However, the adjustment of scanning parameters will have an influence on the performance and image quality of AIDR 3D and temporal averaging in general, and with special regards to the ability of preserving contour sharpness. There are different more approaches to deal with multiple datasets. It would be interesting to compare further approaches with special regards to their influence on image quality parameters in 4D CTP of the myocardium.

As a conclusion, the image quality of 4D dynamic myocardial CTP can be improved by applying AIDR 3D and temporal averaging. With both approaches, the contour sharpness of the myocardium is slightly reduced, but this is less pronounced than the advantageous effect on further objective and subjective image quality parameters. The additional value of applying motion correction on the preservation of contour sharpness and contour details has not been evaluated so far und could provide further advantages if combined with temporal averaging.

**Tables**

**Table 1**

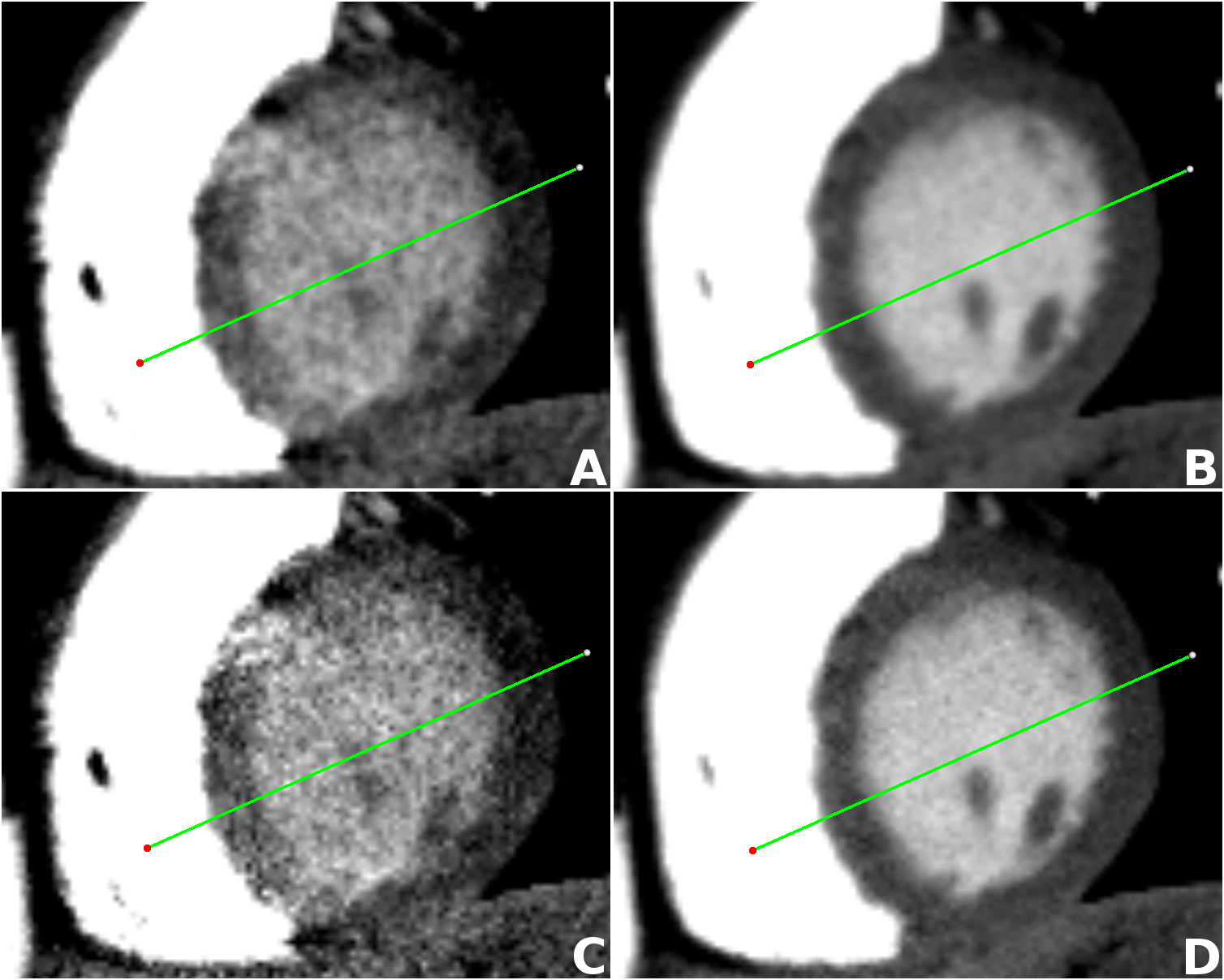
|  |  |  |  |
| --- | --- | --- | --- |
| Feature |  |  |  |
| *Age* |  | 63,7 | ±11,4 |
| *Sex* |  |  |  |
|  | Female | 3 | (10%) |
|  | Male | 26 | (90%) |
| *BMI* |  | 26,5 | ±6,2 |
| *Premedication* | |  |  |
|  | Atenolol | 20 | (69%) |
|  | Dose | 97,5 | ±35,3 |
|  | Ivabradin | 3 | (10%) |
|  | Dose | 6,7 | ±2,9 |
|  | I.v. beta blockers | 6 | (21%) |
|  | Dose | 350,0 | ±207,4 |
| *Angina* |  |  |  |
|  | Typical | 11 | (38%) |
|  | Atypical | 5 | (17%) |
|  | Thoracic pain | 9 | (31%) |
|  | No pain | 4 | (14%) |
|  | Dyspnea | 10 | (34%) |
| *CCS* |  |  |  |
|  | 0 | 12 | (41%) |
|  | I | 6 | (21%) |
|  | II | 9 | (31%) |
|  | III | 2 | (7%) |
| *Cardiac insufficiency* | | 1 | (3%) |
| *Previous myocardial infarct* | | 18 | (62%) |
| *CTA*  mA | | 358,6 | ±59,9 |
| kV | | 119,8 | ±4,7 |
| *CTP*  mA | | 148,3 | ±21,1 |
| kV | | 103,4 | ±7,7 |

**Table 2**



**Figures**

**Figure 1**



**Figure 2**



**Figure 3**

C:\Users\Sarah\Desktop\abb1_klein.tif

**Figure 4**

C:\Users\Sarah\Desktop\abb2.tif

**Figure 5**



**Figure 6**

**Literature**

1. de Roos A, Higgins CB. Cardiac radiology: centenary review. Radiology. 2014;273(2 Suppl):S142-59. doi: 10.1148/radiol.14140432. PubMed PMID: 25340434.

2. Schuetz GM, Zacharopoulou NM, Schlattmann P, Dewey M. Meta-analysis: noninvasive coronary angiography using computed tomography versus magnetic resonance imaging. Ann Intern Med. 2010;152(3):167-77. doi: 10.7326/0003-4819-152-3-201002020-00008. PubMed PMID: 20124233.

3. Ponte M, Bettencourt N, Pereira E, Ferreira ND, Chiribiri A, Schuster A, et al. Anatomical versus functional assessment of coronary artery disease: direct comparison of computed tomography coronary angiography and magnetic resonance myocardial perfusion imaging in patients with intermediate pre-test probability. Int J Cardiovasc Imaging. 2014;30(8):1589-97. doi: 10.1007/s10554-014-0492-y. PubMed PMID: 25082645.

4. Farzaneh-Far A, Steigner M, Kwong RY. Applications and limitations of cardiac computed tomography in the evaluation of coronary artery disease. Coron Artery Dis. 2013;24(7):606-12. doi: 10.1097/MCA.0000000000000027. PubMed PMID: 24077228.

5. Ko SM, Choi JW, Hwang HK, Song MG, Shin JK, Chee HK. Diagnostic Performance of Combined Noninvasive Anatomic and Functional Assessment With Dual-Source CT and Adenosine-Induced Stress Dual-Energy CT for Detection of Significant Coronary Stenosis. AJR Am J Roentgenol. 2012;198(3):512-20. doi: 198/3/512 [pii]

10.2214/AJR.11.7029. PubMed PMID: 22357990.

6. Vavere AL, Simon GG, George RT, Rochitte CE, Arai AE, Miller JM, et al. Diagnostic performance of combined noninvasive coronary angiography and myocardial perfusion imaging using 320 row detector computed tomography: design and implementation of the CORE320 multicenter, multinational diagnostic study. J Cardiovasc Comput Tomogr. 2011;5(6):370-81. doi: 10.1016/j.jcct.2011.11.001. PubMed PMID: 22146496; PubMed Central PMCID: PMCPMC3828643.

7. Bamberg F, Marcus RP, Becker A, Hildebrandt K, Bauner K, Schwarz F, et al. Dynamic myocardial CT perfusion imaging for evaluation of myocardial ischemia as determined by MR imaging. JACC Cardiovasc Imaging. 2014;7(3):267-77. doi: 10.1016/j.jcmg.2013.06.008. PubMed PMID: 24529887.

8. Rochitte CE, George RT, Chen MY, Arbab-Zadeh A, Dewey M, Miller JM, et al. Computed tomography angiography and perfusion to assess coronary artery stenosis causing perfusion defects by single photon emission computed tomography: the CORE320 study. Eur Heart J. 2014;35(17):1120-30. doi: 10.1093/eurheartj/eht488. PubMed PMID: 24255127.

9. George RT, Mehra VC, Chen MY, Kitagawa K, Arbab-Zadeh A, Miller JM, et al. Myocardial CT perfusion imaging and SPECT for the diagnosis of coronary artery disease: a head-to-head comparison from the CORE320 multicenter diagnostic performance study. Radiology. 2014;272(2):407-16. Epub 2014/05/29. doi: 10.1148/radiol.14140806. PubMed PMID: 24865312; PubMed Central PMCID: PMCPMC4263655.

10. Flohr TG, De Cecco CN, Schmidt B, Wang R, Schoepf UJ, Meinel FG. Computed tomographic assessment of coronary artery disease: state-of-the-art imaging techniques. Radiol Clin North Am. 2015;53(2):271-85. doi: 10.1016/j.rcl.2014.11.011. PubMed PMID: 25726993.

11. Williams MC, Newby DE. CT myocardial perfusion imaging: current status and future directions. Clinical radiology. 2016;71(8):739-49. Epub 2016/04/20. doi: 10.1016/j.crad.2016.03.006. PubMed PMID: 27091433.

12. Rossi A, Merkus D, Klotz E, Mollet N, de Feyter PJ, Krestin GP. Stress myocardial perfusion: imaging with multidetector CT. Radiology. 2014;270(1):25-46. Epub 2013/12/21. doi: 10.1148/radiol.13112739. PubMed PMID: 24354374.

13. Sorgaard MH, Kofoed KF, Linde JJ, George RT, Rochitte CE, Feuchtner G, et al. Diagnostic accuracy of static CT perfusion for the detection of myocardial ischemia. A systematic review and meta-analysis. Journal of cardiovascular computed tomography. 2016;10(6):450-7. Epub 2016/10/25. doi: 10.1016/j.jcct.2016.09.003. PubMed PMID: 27773634.

14. Varga-Szemes A, Meinel FG, De Cecco CN, Fuller SR, Bayer RR, Schoepf UJ. CT myocardial perfusion imaging. AJR Am J Roentgenol. 2015;204(3):487-97. doi: 10.2214/AJR.14.13546. PubMed PMID: 25714277.

15. De Cecco CN, Varga-Szemes A, Meinel FG, Renker M, Schoepf UJ. Beyond stenosis detection: computed tomography approaches for determining the functional relevance of coronary artery disease. Radiol Clin North Am. 2015;53(2):317-34. doi: 10.1016/j.rcl.2014.11.009. PubMed PMID: 25726997.

16. Caruso D, Eid M, Schoepf UJ, Jin KN, Varga-Szemes A, Tesche C, et al. Dynamic CT myocardial perfusion imaging. European journal of radiology. 2016;85(10):1893-9. Epub 2016/08/12. doi: 10.1016/j.ejrad.2016.07.017. PubMed PMID: 27510361.

17. Kikuchi Y, Oyama-Manabe N, Naya M, Manabe O, Tomiyama Y, Sasaki T, et al. Quantification of myocardial blood flow using dynamic 320-row multi-detector CT as compared with ¹⁵O-H₂O PET. Eur Radiol. 2014;24(7):1547-56. doi: 10.1007/s00330-014-3164-3. PubMed PMID: 24744200.

18. Feger S, Shaban A, Lukas S, Kendziorra C, Rief M, Zimmermann E, et al. Temporal averaging for analysis of four-dimensional whole-heart computed tomography perfusion of the myocardium: proof-of-concept study. The international journal of cardiovascular imaging. 2016. Epub 2016/11/11. doi: 10.1007/s10554-016-1011-0. PubMed PMID: 27832419.

19. Feger S, Rief M, Zimmermann E, Martus P, Schuijf JD, Blobel J, et al. The Impact of Different Levels of Adaptive Iterative Dose Reduction 3D on Image Quality of 320-Row Coronary CT Angiography: A Clinical Trial. PloS one. 2015;10(5):e0125943. Epub 2015/05/07. doi: 10.1371/journal.pone.0125943. PubMed PMID: 25945924; PubMed Central PMCID: PMCPMC4422621.

20. Enders J, Rief M, Zimmermann E, Asbach P, Diederichs G, Wetz C, et al. High-field open versus short-bore magnetic resonance imaging of the spine: a randomized controlled comparison of image quality. PloS one. 2013;8(12):e83427. Epub 2014/01/07. doi: 10.1371/journal.pone.0083427. PubMed PMID: 24391767; PubMed Central PMCID: PMCPMC3877023.