Received:
14 December 2016

Revised:
29 March 2017

Accepted:
12 April 2017

<https://doi.org/10.1259/bjr.20160933>

Cite this article as:

Benz DC, Gräni C, Hirt Moch B, Mikulicic F, Vontobel J, Fuchs TA, et al. A low-dose and an ultra-low-dose contrast agent protocol for coronary CT angiography in a clinical setting: quantitative and qualitative comparison to a standard dose protocol. *Br J Radiol* 2017; **90**: 20160933.

FULL PAPER

A low-dose and an ultra-low-dose contrast agent protocol for coronary CT angiography in a clinical setting: quantitative and qualitative comparison to a standard dose protocol

DOMINIK C BENZ, MD, CHRISTOPH GRÄNI, MD, BEATRICE HIRT MOCH, MD, FRAN MIKULICIC, MD, JAN VONTOBEL, MD, TOBIAS A FUCHS, MD, JULIA STEHLI, MD, OLIVIER F CLERC, MD, MATHIAS POSSNER, MD, AJU P PAZHENKOTTIL, MD, OLIVER GAEMPERLI, MD, RONNY R BUECHEL, MD and PHILIPP A KAUFMANN, MD

Department of Nuclear Medicine, Cardiac Imaging, University Hospital Zurich, Zurich, Switzerland

Address correspondence to: Dr Ronny R Buechel

E-mail: ronny.buechel@usz.ch

The authors Dominik C Benz and Christoph Gräni share the first authorship. The authors Ronny R Buechel and Philipp A Kaufmann share the last authorship.

Objective: To evaluate the impact of a low-dose (LD) and an ultra-LD (ULD) contrast protocol for coronary CT angiography on qualitative and quantitative image parameters in a clinical setting.

Methods: We scanned 120 consecutive patients with a 256-slice CT scanner applying a LD (60 patients, 35–55 ml) or ULD (60 patients, 25–45 ml) contrast protocol adapted to the body mass index. Visually assessed image quality and attenuation measured in each coronary segment were retrospectively compared in 20 consecutive patients scanned with a normal-dose (ND, 40–105 ml) contrast protocol.

Results: Visually assessed image quality did not differ significantly among protocols. By contrast, attenuation obtained from the ULD protocol (median contrast volume 35 ml) differed significantly from the LD (median 45 ml) and ND (median 70 ml) protocols in the

coronary segments (316 ± 52 vs 363 ± 60 and 359 ± 52 HU, $p < 0.001$). Attenuation did not differ significantly between the LD and ND protocol. The proportion of patients with inadequate coronary vessel attenuation was significantly higher ($p < 0.001$) in the ULD protocol (37%) than in the ND (5%) and LD (10%) protocols but did not differ significantly between the ND and LD protocols.

Conclusion: In a clinical setting, a LD contrast protocol with a median volume of 45 ml is feasible for the latest generation 256-slice coronary CT angiography as it yields attenuation comparable to a ND protocol. By contrast, the implementation of an ULD protocol remains challenging.

Advances in knowledge: Although not perceived by the naked eye, an ULD contrast protocol in a clinical setting yields attenuation below a threshold for diagnostic image quality.

INTRODUCTION

Coronary CT angiography (CCTA) has become a reliable and accurate tool for non-invasive exclusion of significant coronary artery disease. Its widespread clinical use, however, has raised concerns about the potential risks associated with increased exposure to ionizing radiation.¹ With the implementation of prospective electrocardiography-triggering, iterative reconstruction algorithms and wide-volume scanners radiation dose exposure could be substantially decreased.^{2,3} The debate on the potential risks, therefore, has been extended to additional aspects of CCTA, and contrast agent exposure has been identified as a significant contributor, including allergic reactions and potentially also contrast-

induced nephropathy.⁴ Of particular importance, a dose-dependent association with contrast-induced nephropathy has been suggested.^{5–7} Since wide-volume scanners and high-pitch CT protocols enable CCTA acquisition within a single heartbeat, acquisition time can be shortened to <0.3 s. Furthermore, a more powerful tube allows acquisition at voltages of 100 kVp or below, thus yielding higher contrast than the standard 120-kVp technique. As a consequence, the contrast agent volume was reportedly reduced to 40 ml or even less.^{8–12} These results, however, were based on scans within research protocols in selected patients and do not reflect daily clinical practice where high image quality is needed consistently and independent of a patient's body

habitus. Therefore, previous reports have called for future studies that evaluate individually tailored contrast agent protocols,⁸ ideally adapted to the body mass index (BMI).¹³

After implementation of a latest-generation 256-slice CT scanner at the University Hospital Zurich, a previously validated contrast agent protocol¹⁴ was customized and contrast volumes were lowered as suggested by recent publications^{8–12} while image quality was assessed through visual assessment. The aim of the present study was to evaluate the impact of a low-dose (LD) and an ultra-LD (ULD) BMI-adapted contrast agent protocol on qualitative and quantitative image parameters in an unselected clinical patient population and to compare it with a standard contrast agent protocol.

METHODS AND MATERIALS

Patient population

From an institutional scientific registry for evaluation of CCTA acquired on a latest-generation 256-slice CT scanner (Revolution CT; GE Healthcare, Waukesha, WI), we retrospectively identified 60 consecutive patients who were scanned with a low-dose contrast agent protocol (LD protocol) and 60 consecutive patients who were scanned with an ultra-low-dose contrast agent protocol (ULD protocol). Quantitative and qualitative image parameters of the ULD and LD scans were then compared in 20 consecutive patients scanned with a previously established standard normal-dose (ND) BSA-adapted contrast agent protocol (ND protocol, Table 1).¹⁴ All patients were referred for clinically indicated CCTA due to known or suspected coronary artery disease. The study was approved by the local ethics committee (KEK-ZH No. 214–0632), and all patients provided written informed consent.

Image acquisition

All patients underwent contrast-enhanced CCTA during breath-hold at inspiration with prospective electrocardiography triggering at 75% of the R-R interval on a latest generation 256-slice high-resolution CT scanner (Revolution CT). Up to 30 mg of metoprolol (Beloc-Zok; AstraZeneca, London, UK) was administered intravenously prior to the examination if the heart rate was >65 beats min^{-1} in order to obtain optimal image quality for CCTA.¹⁵ Patients received 0.4 mg sublingual

isosorbiddinitrate (Isoket®; Schwarz Pharma, Monheim, Germany) 2 min prior to the CCTA scan.

Iodixanol (Visipaque 320, 320mg ml^{-1} ; GE Healthcare, Buckinghamshire, UK) was injected into an antecubital vein followed by 50 ml of saline solution via an 18-gauge catheter. For the LD and the ULD protocols, contrast agent volume and flow rate were adapted to the BMI (Table 2). Similarly, for CCTA acquisition, tube voltage (80–120 kVp) and tube current (180–310 mA) were adapted to the BMI according to our clinical routine.³ A collimation of 256×0.625 mm resulting in a maximum z-coverage of 16 cm was individualized to the patient's topogram and used with a display field of view of 25 cm. All scans were acquired in high resolution mode with an in-plane spatial resolution of 0.23×0.23 mm. Gantry rotation time was 280 ms. Image acquisition was triggered after the signal density reached a visually detectable threshold in the ascending aorta (bolus tracking). CT raw data were reconstructed with adaptive statistical iterative reconstruction algorithm (ASiR-V™; GE Healthcare).¹⁶ Radiation dose for CCTA was determined by the dose-length product multiplied by a conversion factor of $0.014 \text{ mSv mGy}^{-1} \text{ cm}^{-1}$.¹⁷

Quantitative image analysis

On a dedicated workstation (Advantage workstation 4.6; GE Healthcare), for every patient, the aortic root was examined at the level of the left main coronary artery (LMA) on an axial image using a region of interest (ROI) with a 20-mm diameter to measure mean attenuation (representing signal) and its standard deviation (representing noise) in Hounsfield units (HU). Similarly, measurements of the mean attenuation in the proximal part of every coronary segment were obtained using the smallest possible ROI with 1-mm diameter on axial images and due care was taken to avoid calcifications and streak artefacts. If the segment was too small for the ROI to fit in, the segment was considered non-evaluable. Attenuation in the LMA and proximal right coronary artery (RCA) was measured using a ROI with a 2-mm diameter and the mean between the attenuation in the LMA and proximal RCA was computed. To calculate contrast-to-noise ratio (CNR), for which noise was defined as the standard deviation of attenuation in the aortic root, an additional ROI with 2-mm diameter was placed in the

Table 1. Validated standard protocol

BSA (m^2)	Contrast volume (mL)	Flow rate (mL s^{-1})
<1.70	40	3.5
1.70–1.79	45	4.0
1.80–1.94	60	4.0
1.95–2.04	80	4.5
2.05–2.14	80	5.0
2.15–2.14	85	5.0
2.25–2.49	95	5.0
≥ 2.5	105	5.0

BSA, body surface area.

Table 2. Body mass index (BMI)-adapted contrast protocols

BMI (kg m^{-2})	Contrast volume (mL)		Flow rate (mL s^{-1})
	LD	ULD	ULD and LD
<20.0	35	25	3.5
20.0–22.4	40	30	4.0
22.5–24.9	40	30	4.0
25.0–27.4	45	35	4.5
27.5–29.9	50	40	5.0
>30.0	55	45	5.0

LD, low-dose protocol; ULD, ultra-low-dose protocol.

adjacent perivascular tissue on axial images. The proportion of segments with attenuation <300 HU was calculated and compared among protocols. In addition, the proportion of patients with mean proximal attenuation <326 HU was calculated and compared among protocols. These two thresholds (*i.e.* 300 and 326 HU, respectively) have been demonstrated as the lower threshold for obtaining diagnostic image quality in coronary segments⁸ and overall patients,^{18,19} respectively.

Qualitative image analysis

Qualitative image assessment was performed visually by two independent readers experienced in CCTA analysis (DCB and CG). The reconstructed images were transferred to a dedicated workstation (Advantage workstation 4.6) and presented to each reader in a randomized order to ensure blinding of the readers to protocol allocation. Coronary arteries were subdivided into 15 segments.²⁰ Axial image stacks were

Table 3. Patient characteristics and scan parameters by protocol

Characteristic	ND protocol	LD protocol	ULD protocol	Overall	<i>p</i> -value
Male gender (%)	60	62	60	61	0.851
Age (years)	59 ± 11	56 ± 12	55 ± 12	56 ± 12	0.527
BMI (kg m ^{−2})	26.0 ± 3.5	25.9 ± 5.4	25.7 ± 5.4	25.8 ± 4.6	0.960
Heart rate during CT scan (beats min ^{−1})					
Median/Interquartile range	61	57	57	58	0.434
Median/Interquartile range	56–66	51–63	49–65	54–61	
Tube current (mA)					
Median/Interquartile range	290	290	290	290	0.794
Median/Interquartile range	250–330	250–330	225–355	230–310	
Tube voltage (kV)					
Median/Interquartile range	100	100	100	100	0.550
Median/Interquartile range	100–100	100–100	100–100	100–100	
Median/Interquartile range	80–120	80–120	80–120	80–120	
Radiation dose (mSv)					
Median/Interquartile range	0.56	0.53	0.48	0.51	0.492
Median/Interquartile range	0.37–0.75	0.33–0.73	0.29–0.67	0.40–0.61	
Contrast agent flow (mL s ^{−1})					
Median/Interquartile range	4.3	4.5	4.5	4.5	0.625
Median/Interquartile range	3.6–5.0	4.0–5.0	4.0–5.0	4.0–5.0	
Contrast agent volume (mL)					
Median/Interquartile range	70	45	35	40	<0.001
Median/Interquartile range	51–89	35–55	25–45	35–45	

ND, normal-dose; LD, low-dose; ULD, ultra-low-dose; BMI, body mass index. Values given are mean ± standard deviation if not otherwise specified.

reviewed and each coronary artery segment large enough for the smallest possible ROI to fit in was evaluated. Small coronary segments were defined as segments 3, 4, 8, 9, 10, 12, 13, 14 and 15.¹⁵ Image quality regarding vessel opacification was assessed using a four-point scale at a window level of 800 HU and a window width of 300 HU:²¹ 1 = poor vessel opacification resulting in a non-assessable coronary segment; 2 = satisfactory vessel opacification with maintained low-contrast resolution; 3 = good vessel opacification with adequate vessel delineation; and 4 = excellent vessel opacification with distinct vessel delineation. The mean value of the image quality scores between the two readers was used for statistical analysis.

Statistical analysis

Quantitative variables are expressed as mean $\pm$ standard deviation or as median with interquartile range if not normally distributed. Categorical variables are expressed as frequencies or percentages. The data were tested for normal distribution using the Kolmogorov–Smirnov test. Comparison among protocols was performed using one-way analysis of variance, and *post hoc* pairwise *t*-tests were adjusted for multiple comparisons by the Bonferroni correction. Non-parametric variables were compared using the Kruskal–Wallis test. The independent-samples *t*-test was used to compare continuous variables. The χ^2 test was used to evaluate proportions of categorical data. To assess the correlation between different variables, Spearman rank correlation was applied. Interrater agreement was assessed using intraclass correlation analysis. SPSS® v. 20.0 (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL) was used for analysis. A *p*-value <0.05 was considered statistically significant.

RESULTS

Study population and coronary CT angiography parameters

CCTA was successfully performed in all 140 patients. Patient baseline characteristics and scan parameters did not differ across protocols (Table 3). Of note, the mean BMI was $25.8 \pm 4.6 \text{ kg m}^{-2}$, including a wide range of $17.8\text{--}45.2 \text{ kg m}^{-2}$, with no differences across protocols ($p = 0.960$). By contrast, the administered median contrast agent volume significantly decreased from the ND protocol to the LD and ULD protocols (Table 3, $p < 0.001$).

Quantitative image analysis

Results of the quantitative analysis are presented in Table 4. Of note, attenuation differed significantly across protocols, and *post hoc* comparisons revealed significantly lower mean attenuation in the aortic root as well as in the coronary segments for the ULD protocol compared with the ND and LD protocols ($p < 0.001$). Between the ND and LD protocols, however, there were no significant differences in the mean attenuation. When large and small coronary segments were analyzed separately, the mean attenuation in the aortic root and in the coronary segments was still significantly lower for the ULD protocol than for the ND and LD protocols ($p < 0.001$). Furthermore, the mean attenuation was significantly higher for large coronary segments than for small coronary segments in each protocol ($p < 0.001$). The mean attenuation of the ND, LD and ULD protocols is illustrated in Figure 1a for proximal, mid and distal segments separately. There were significantly less segments with attenuation <300 HU for the ND (30%) and LD protocol (29%) compared with the ULD protocol (45%, $p < 0.001$). On a patient level, the proportion of patients with mean proximal attenuation <326 HU was significantly higher in the ULD protocol (37%) than in the ND and LD protocols ($p < 0.001$). However, the proportion did not differ

Table 4. Image analysis by protocol

Characteristic	ND protocol	LD protocol	ULD protocol	<i>p</i> -value
Quantitative analysis				
Attenuation, mean HU $\pm$ SD				
Aortic root	490 $\pm$ 80	472 $\pm$ 102	410 $\pm$ 65	$<0.001^a$
All coronary segments	359 $\pm$ 52	363 $\pm$ 60	316 $\pm$ 52	$<0.001^a$
Small coronary segments	307 $\pm$ 47	319 $\pm$ 47	276 $\pm$ 50	$<0.001^a$
Large coronary segments	419 $\pm$ 63	417 $\pm$ 82	364 $\pm$ 75	$<0.001^a$
CNR, mean $\pm$ SD				
LMA	18 $\pm$ 2	16 $\pm$ 3	17 $\pm$ 3	0.113
RCA	17 $\pm$ 3	16 $\pm$ 3	17 $\pm$ 3	0.101
Qualitative analysis				
Image quality, mean $\pm$ SD				
All coronary segments	3.43 $\pm$ 0.28	3.48 $\pm$ 0.20	3.38 $\pm$ 0.29	0.191
Small coronary segments	3.11 $\pm$ 0.36	3.15 $\pm$ 0.30	3.02 $\pm$ 0.38	0.108
Large coronary segments	3.85 $\pm$ 0.23	3.91 $\pm$ 0.13	3.85 $\pm$ 0.23	0.399

CNR, contrast-to-noise ratio; HU, Hounsfield units; LD, low-dose; LMA, left main coronary artery; ND, normal-dose; SD, standard deviation; ULD, ultra-low-dose; RCA, right coronary artery.

^a*Post hoc t*-test with Bonferroni correction revealed no significant difference between the ND and LD protocols.

Figure 1. The mean attenuation (a) and image quality (b) for large and small coronary segments are illustrated for each protocol separately. Numbers in each bar are the mean attenuation in Hounsfield units (a) or mean image quality (b). Error bars indicate 95% confidence interval. Asterisks identify $p < 0.001$ vs ultra-low-dose protocol.

between the ND (5%) and LD (10%) protocols ($p = 0.493$). Across all protocols, in the population with mean proximal attenuation < 326 HU, the CNR was significantly lower in the LMA and RCA than in the population with mean proximal attenuation > 326 HU ($p < 0.001$). Nonetheless, the proportion of non-evaluable segments did not significantly differ across protocols (ND 7%, ULD 9%, LD 7%; $p = 0.271$).

Lastly, the CNR did not differ significantly across protocols neither in the LMA nor in the RCA ($p = 0.113$ and $p = 0.101$, respectively).

Qualitative image analysis

An overview on the qualitative image analysis is given in Table 4. In 140 patients, a total of 1936 coronary artery segments were evaluated (92.2% of theoretically 2100 possible segments in 140 patients with 15 segments). Interrater reliability for image quality assessment was good (ICC: 0.796). Although the mean image quality of all segments was lower for the ULD protocol than for the ND and LD protocols, there was no significant difference across protocols ($p = 0.191$). Image quality of the ND, LD and ULD protocols is visualized separately in Figure 1b for proximal, mid and distal segments. In a subgroup analysis, when

Figure 2. The body mass index (BMI) did not correlate with attenuation in any of the protocols: normal-dose (ND) protocol $r = -0.171$, $p = 0.472$; low-dose (LD) protocol $r = -0.069$, $p = 0.601$; ultra-low-dose (ULD) protocol $r = -0.113$, $p = 0.392$. Attenuation was defined as the mean attenuation of left main artery (LMA) and right coronary artery (RCA).

the mean image quality was analyzed separately in large and small segments, still no significant difference across protocols was found ($p = 0.399$ and $p = 0.108$, respectively). Nevertheless, the mean image quality in large segments was rated significantly better than the mean image quality of small segments ($p < 0.001$), affirming the internal validity of image quality assessment.

Determinates of attenuation and image quality

No correlation was found between attenuation in the aortic root and BMI (ND protocol: $r = -0.171$, $p = 0.472$; ULD protocol: $r = -0.113$, $p = 0.392$; LD protocol: $r = -0.069$, $p = 0.601$) (Figure 2).

Image quality was rated significantly lower (2.91 ± 0.69) for coronary segments with attenuation below a threshold of 300 HU ($n = 699$) compared with coronary segments with attenuation above this threshold ($n = 1237$; 3.73 ± 0.46 ; $p < 0.001$) (Figure 3).

Scan acquisition was timed well since attenuation peaked in the aortic root in all three contrast protocols (Table 5). No

Figure 3. Box plots of visually assessed image quality of coronary segments grouped by attenuation below or above 300 HU. Image quality for coronary segments with attenuation below a threshold of 300 HU was significantly lower than for coronary segments with attenuation above this threshold ($p < 0.001$). Horizontal black line and grey boxes indicate median and interquartile range. Whiskers depict 1.5 times the interquartile range.

significant differences in attenuation between the ND and LD protocols were found in the left atrium (440 vs 434 HU), apex (479 vs 467 HU), left ventricle outflow tract (474 vs 465 HU), aortic root (490 vs 472 HU) and descending aorta (494 vs 445 HU). Conversely, in the ULD protocol, attenuation was significantly lower at all locations (378, 400, 404, 410 and 383 HU, respectively) than in the ND or LD protocols.

DISCUSSION

In the present study, a BMI-adapted contrast agent protocol allowed significant reduction of median contrast agent volume from 70 to 45 ml without decrease of attenuation in the aortic root, in large and in small coronary segments and without compromising visually assessed vessel opacification. Although no visually perceivable change in vessel attenuation was noted when median contrast agent volume was reduced from 70 to

Table 5. Timing of scan acquisition by protocols

Location	ND protocol	LD protocol	ULD protocol	<i>p</i> -value
Left atrium	440 ± 122	434 ± 120	378 ± 112	0.019 ^a
Apex	479 ± 77	467 ± 101	400 ± 99	<0.001 ^a
Left ventricle outflow tract	474 ± 82	465 ± 105	404 ± 97	0.001 ^a
Aortic root	490 ± 80	472 ± 102	410 ± 95	<0.001 ^a
Descending aorta	494 ± 81	445 ± 93	383 ± 79	<0.001 ^a

ND, normal-dose; LD, low-dose; ULD, ultra-low-dose.

^aPost hoc *t*-test with Bonferroni correction revealed no significant difference between the ND and LD protocols.

Figure 4. Examples of three left anterior descending arteries compared in the three different contrast protocols. Although no changes in image quality can be perceived, attenuation differs substantially between the patients scanned with normal-dose (a) or low-dose protocol (b) and the patient scanned with the ultra-low-dose protocol (c). (a) A 61-year-old male with a body mass index of 22 kg m^{-2} was scanned at a heart rate 64/min with the normal-dose protocol (e.g. 60 ml at a flow rate of 4 ml s^{-1}) and had a proximal attenuation of 347 HU. (b) A 49-year-old male with a body mass index of 23 kg m^{-2} was scanned at a heart rate of 58 beats/min with the low-dose protocol (e.g. 40 ml at a flow rate of 4 ml s^{-1}) and had a proximal attenuation of 349 HU. (c) A 69-year-old male with a body mass index 21 kg m^{-2} was scanned at a heart rate 54 beats/min with the ultra-low-dose protocol (e.g. 30 ml at a flow rate of 4 ml s^{-1}) and had a proximal attenuation of 301 HU.

35 ml, attenuation as measured in the aortic root and in the coronary segments was significantly reduced.

Although it is evident that a contrast agent protocol needs to yield sufficient image quality, the literature assessing the optimal characteristics of a contrast agent protocol for CCTA has shifted its focus from qualitative to quantitative assessment of vessel attenuation.^{18,19} Although the conclusions brought forth by these studies remain inconsistent, they highlight the significance of assessing image quality not only visually but also quantitatively. Firstly, it may be perceived as a mandatory requirement for any protocol to yield vessel attenuation that is not relevantly influenced by BMI.^{22,23} In contrast to previous reports in similar settings,²⁴ the BMI-adapted contrast protocols in the present study including patients over a broad range of BMI (17.8–45.2 kg m⁻²) have demonstrated no changes in attenuation with increasing BMI. This reflects that our BMI-adapted contrast volume protocol successfully compensates for the BMI-related interindividual differences in coronary attenuation. As image noise increases and coronary vessel attenuation decreases with higher BMI, if tube current and voltage are kept constant, we have combined the BMI-adapted contrast volume protocol with a BMI-adapted tube current and voltage protocol.²⁵ The current Society of Cardiovascular Computed Tomography guidelines for performance of CCTA recommend a minimal vessel attenuation of 250 HU,²⁶ a threshold based on a study performed using a four-slice CT scanner.²⁷ However, more recent studies have consistently found that attenuation values >326 HU yield better visualization associated with improved diagnostic accuracy for detection of coronary artery stenosis^{18,19}—mainly driven by a lower rate of false-positive findings. The reduced specificity for patients with attenuation values <326 HU has been linked to an overestimation of stenosis severity as a consequence of reduced contrast-to-noise ratio and, hence, reduced sharpness of vessel visualization. Another study documented attenuation values >300 HU as a determinant of visual image quality on a segmental basis.⁸ In the present study, the proportion of segments with inadequate attenuation values (according to these previously defined thresholds) remained unchanged with the LD protocol compared with the ND protocol. These proportions, on the contrary, were significantly increased with the ULD protocol. Moreover, a phantom study has demonstrated that attenuation that is too high causes significant underestimation of stenosis in smaller vessels while lower attenuation induces slight but clinically acceptable overestimation of stenosis.²⁸ In view of the evidence that intracoronary attenuation significantly impacts plaque assessment,^{29,30} the appropriate level of vessel attenuation seems fundamental to ensure state-of-the-art CCTA imaging.

In the present study, the mean attenuation of all coronary segments was 359 and 363 HU for the ND and LD protocols but was significantly lower at 316 HU for the ULD protocol. Although the attenuation found in the LD and ND groups lie well within this optimal range of coronary opacification, the attenuation in the ULD group is substantially lower. Therefore, these findings indicate that the shortened acquisition time with wide-volume CT scanners (acquiring the whole heart within one beat)

allows a reduction of the injected contrast volume by about 35% (*i.e.* from a median volume of 70 to 45 ml) compared with 64-slice CT scanners. However, in contrast to previous studies that were performed in selected patients,^{8–12} the present study questions the clinical feasibility of a reduction by 50% and beyond (*i.e.* from 70 to 35 ml). It might be speculated that a reduction of 35% just shortens the length of the contrast bolus without affecting the peak attenuation. Conversely, a reduction of 50% might not only reduce the length of the contrast bolus but also its peak attenuation.

Although a significant decrease in measured attenuation occurred with the ULD protocol, qualitative image parameters remained similar across all protocols. Since the LD and ULD contrast agent protocols were customized at our institution by visual feedback of the scan quality, the finding that no qualitative differences were found is not surprising. This may in part be explained by the fact that overall CCTA image quality was already good to excellent, rendering it difficult to reveal visually detectable and statistically significant differences. However, considering the evidence that reduced vessel attenuation results in a clinically relevant deterioration of diagnostic accuracy, the present study implies that when a novel contrast agent protocol is implemented into clinical routine, qualitative evaluation is not sufficient to ensure state-of-the-art CCTA imaging (Figure 4). As a consequence, although ULD contrast protocols were feasible in research settings, their implementation into clinical routine remains challenging.

We acknowledge the following limitation to our study. Owing to the lack of a standard of reference, we cannot comment on the impact on diagnostic accuracy. However, the aim of this study was to assess the performance of different contrast agent protocols in terms of obtained vessel attenuation rather than the impact of vessel attenuation on diagnostic accuracy in general. Furthermore, since both tube voltage and iodine delivery rate were adapted to the BMI, their impact on attenuation could not be analyzed independently. In addition, our results may not necessarily be applicable to data sets acquired on scanners unable to perform isothermal coverage of the heart (*e.g.* 64-slice or 128-slice CT scanners). Although the standard ND contrast protocol was validated on a 64-slice CT scanner, it was still adjusted according to anthropometric patient measurement (*e.g.* BSA) to individualize coronary contrast opacification.

CONCLUSION

In a clinical setting, a LD contrast protocol with a median volume of 45 ml is feasible for the latest-generation 256-slice CCTA, as it yields attenuation comparable to a ND protocol. By contrast, the implementation of an ULD protocol remains challenging.

ACKNOWLEDGMENTS

The authors thank Verena Weichselbaumer, Martina Vogt, Tania Lagrange, Kevin Frei and Lasien Vojo for their excellent technical support. The University Hospital Zurich holds a research agreement with GE Healthcare.

REFERENCES

- Sodickson A, Baeyens PF, Andriole KP, Prevedello LM, Nawfel RD, Hanson R, et al. Recurrent CT, cumulative radiation exposure, and associated radiation-induced cancer risks from CT of adults. *Radiology* 2009; **251**: 175–84. doi: <https://doi.org/10.1148/radiol.2511081296>
- Buechel RR, Husmann L, Herzog BA, Pazhenkottil AP, Nkoulou R, Ghadri JR, et al. Low-dose computed tomography coronary angiography with prospective electrocardiogram triggering: feasibility in a large population. *J Am Coll Cardiol* 2011; **57**: 332–6. doi: <https://doi.org/10.1016/j.jacc.2010.08.634>
- Benz DC, Gräni C, Hirt Moch B, Mikulicic F, Vontobel J, Fuchs TA, et al. Minimized radiation and contrast agent exposure for coronary computed tomography angiography: first clinical experience on a latest generation 256-slice scanner. *Acad Radiol* 2016; **23**: 1008–14. doi: <https://doi.org/10.1016/j.acra.2016.03.015>
- Knuuti J, Bengel F, Bax JJ, Kaufmann PA, Le Guludec D, Perrone Filardi P, et al. Risks and benefits of cardiac imaging: an analysis of risks related to imaging for coronary artery disease. *Eur Heart J* 2014; **35**: 633–8. doi: <https://doi.org/10.1093/eurheartj/ehf512>
- Toprak O. Conflicting and new risk factors for contrast induced nephropathy. *J Urol* 2007; **178**: 2277–83. doi: <https://doi.org/10.1016/j.juro.2007.08.054>
- Gruberg L, Mintz GS, Mehran R, Gangas G, Lansky AJ, Kent KM, et al. The prognostic implications of further renal function deterioration within 48 h of interventional coronary procedures in patients with pre-existent chronic renal insufficiency. *J Am Coll Cardiol* 2000; **36**: 1542–8.
- Thomsen HS, Morcos SK. Risk of contrast-medium-induced nephropathy in high-risk patients undergoing MDCT—a pooled analysis of two randomized trials. *Eur Radiol* 2009; **19**: 891–7. doi: <https://doi.org/10.1007/s00330-008-1206-4>
- Lembcke A, Schwenke C, Hein PA, Knobloch G, Durmus T, Hamm B, et al. High-pitch dual-source CT coronary angiography with low volumes of contrast medium. *Eur Radiol* 2014; **24**: 120–7. doi: <https://doi.org/10.1007/s00330-013-2988-6>
- Hein PA, May J, Rogalla P, Butler C, Hamm B, Lembcke A. Feasibility of contrast material volume reduction in coronary artery imaging using 320-slice volume CT. *Eur Radiol* 2010; **20**: 1337–43. doi: <https://doi.org/10.1007/s00330-009-1692-z>
- Tatsugami F, Matsuki M, Inada Y, Kanazawa S, Nakai G, Takeda Y, et al. Feasibility of low-volume injections of contrast material with a body weight-adapted iodine-dose protocol in 320-detector row coronary CT angiography. *Acad Radiol* 2010; **17**: 207–11. doi: <https://doi.org/10.1016/j.acra.2009.09.010>
- Zhang F, Yang L, Song X, Li YN, Jiang Y, Zhang XH, et al. Feasibility study of low tube voltage (80 kVp) coronary CT angiography combined with contrast medium reduction using iterative model reconstruction (IMR) on standard BMI patients. *Br J Radiol* 2016; **89**: 20150766. doi: <https://doi.org/10.1259/bjr.20150766>
- Iyama Y, Nakaura T, Yokoyama K, Kidoh M, Harada K, Oda S, et al. Low-contrast and low-radiation dose protocol in cardiac computed tomography: usefulness of low tube voltage and knowledge-based iterative model reconstruction algorithm. *J Comput Assist Tomogr* 2016; **40**: 941–7. doi: <https://doi.org/10.1097/RCT.0000000000000440>
- Zhu X, Zhu Y, Xu H, Yang G, Tang L, Xu Y. Dual-source CT coronary angiography involving injection protocol with iodine load tailored to patient body weight and body mass index: estimation of optimal contrast material dose. *Acta Radiol* 2013; **54**: 149–55. doi: <https://doi.org/10.1258/ar.2012.120362>
- Pazhenkottil AP, Husmann L, Buechel RR, Herzog BA, Nkoulou R, Burger IA, et al. Validation of a new contrast material protocol adapted to body surface area for optimized low-dose CT coronary angiography with prospective ECG-triggering. *Int J Cardiovasc Imaging* 2010; **26**: 591–7. doi: <https://doi.org/10.1007/s10554-010-9594-3>
- Husmann L, Valenta I, Gaemperli O, Adda O, Treyer V, Wyss CA, et al. Feasibility of low-dose coronary CT angiography: first experience with prospective ECG-gating. *Eur Heart J* 2008; **29**: 191–7. doi: <https://doi.org/10.1093/eurheartj/ehm613>
- Benz DC, Grani C, Mikulicic F, Vontobel J, Fuchs TA, Possner M, et al. Adaptive statistical iterative reconstruction-V: impact on image quality in ultralow-dose coronary computed tomography angiography. *J Comput Assist Tomogr* 2016; **40**: 958–63. doi: <https://doi.org/10.1097/rct.0000000000000460>
- Hausleiter J, Meyer T, Hermann F, Hadamitzky M, Krebs M, Gerber TC, et al. Estimated radiation dose associated with cardiac CT angiography. *JAMA* 2009; **301**: 500–7. doi: <https://doi.org/10.1001/jama.2009.54>
- Cademartiri F, Maffei E, Palumbo AA, Malagó R, La Grutta L, Meijboom WB, et al. Influence of intra-coronary enhancement on diagnostic accuracy with 64-slice CT coronary angiography. *Eur Radiol* 2008; **18**: 576–83. doi: <https://doi.org/10.1007/s00330-007-0773-0>
- Cademartiri F, Mollet NR, Lemos PA, Saia F, Midiri M, de Feyter PJ, et al. Higher intra-coronary attenuation improves diagnostic accuracy in MDCT coronary angiography. *AJR Am J Roentgenol* 2006; **187**: W430–3. doi: <https://doi.org/10.2214/ajr.05.1406>
- Austen WG, Edwards JE, Frye RL, Gensini GG, Gott VL, Griffith LS, et al. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. *Circulation* 1975; **51**(Suppl. 4): 5–40. doi: <https://doi.org/10.1161/01.cir.51.4.5>
- Leipsic J, Abbata S, Achenbach S, Cury R, Earls JP, Mancini GJ, et al. SCCT guidelines for the interpretation and reporting of coronary CT angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. *J Cardiovasc Comput Tomogr* 2014; **8**: 342–58. doi: <https://doi.org/10.1016/j.jcct.2014.07.003>
- Husmann L, Herzog BA, Burkhard N, Valenta I, Burger IA, Gaemperli O, et al. Low-dose coronary CT angiography with prospective ECG triggering: validation of a contrast material protocol adapted to body mass index. *AJR Am J Roentgenol* 2009; **193**: 802–6. doi: <https://doi.org/10.2214/ajr.08.2052>
- Husmann L, Alkadhi H, Boehm T, Leschka S, Schepis T, Koepfli P, et al. Influence of cardiac hemodynamic parameters on coronary artery opacification with 64-slice computed tomography. *Eur Radiol* 2006; **16**: 1111–6. doi: <https://doi.org/10.1007/s00330-005-0110-4>
- Kumamaru KK, Steigner ML, Soga S, Signorelli J, Bedayat A, Adams K, et al. Coronary enhancement for prospective ECG-gated single R-R axial 320-MDCT angiography: comparison of 60- and 80-mL iopamidol 370 injection. *AJR Am J Roentgenol* 2011; **197**: 844–50. doi: <https://doi.org/10.2214/AJR.10.5980>
- Tatsugami F, Husmann L, Herzog BA, Burkhard N, Valenta I, Gaemperli O, et al.

- Evaluation of a body mass index-adapted protocol for low-dose 64-MDCT coronary angiography with prospective ECG triggering. *AJR Am J Roentgenol* 2009; **192**: 635–8. doi: <https://doi.org/10.2214/AJR.08.1390>
26. Abbara S, Arbab-Zadeh A, Callister TQ, Desai MY, Mamuya W, Thomson L, et al. SCCT guidelines for performance of coronary computed tomographic angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. *J Cardiovasc Comput Tomogr* 2009; **3**: 190–204. doi: <https://doi.org/10.1016/j.jcct.2009.03.004>
27. Becker CR, Hong C, Knez A, Leber A, Bruening R, Schoepf UJ, et al. Optimal contrast application for cardiac 4-detector-row computed tomography. *Invest Radiol* 2003; **38**: 690–4. doi: <https://doi.org/10.1097/01.rli.0000084886.44676.e4>
28. Fei X, Du X, Yang Q, Shen Y, Li P, Liao J, et al. 64-MDCT coronary angiography: phantom study of effects of vascular attenuation on detection of coronary stenosis. *AJR Am J Roentgenol* 2008; **191**: 43–9. doi: <https://doi.org/10.2214/ajr.07.2653>
29. Cademartiri F, Mollet NR, Runza G, Bruining N, Hamers R, Somers P, et al. Influence of intracoronary attenuation on coronary plaque measurements using multislice computed tomography: observations in an *ex vivo* model of coronary computed tomography angiography. *Eur Radiol* 2005; **15**: 1426–31. doi: <https://doi.org/10.1007/s00330-005-2697-x>
30. Cademartiri F, Runza G, Palumbo A, Maffei E, Martini C, McFadden E, et al. Lumen enhancement influences absolute noncalcific plaque density on multislice computed tomography coronary angiography: *ex-vivo* validation and *in-vivo* demonstration. *J Cardiovasc Med (Hagerstown)* 2010; **11**: 337–44. doi: <https://doi.org/10.2459/JCM.0b013e3283312400>