Individual optimisation of contrast media application and radiation dose in computed tomographic angiography

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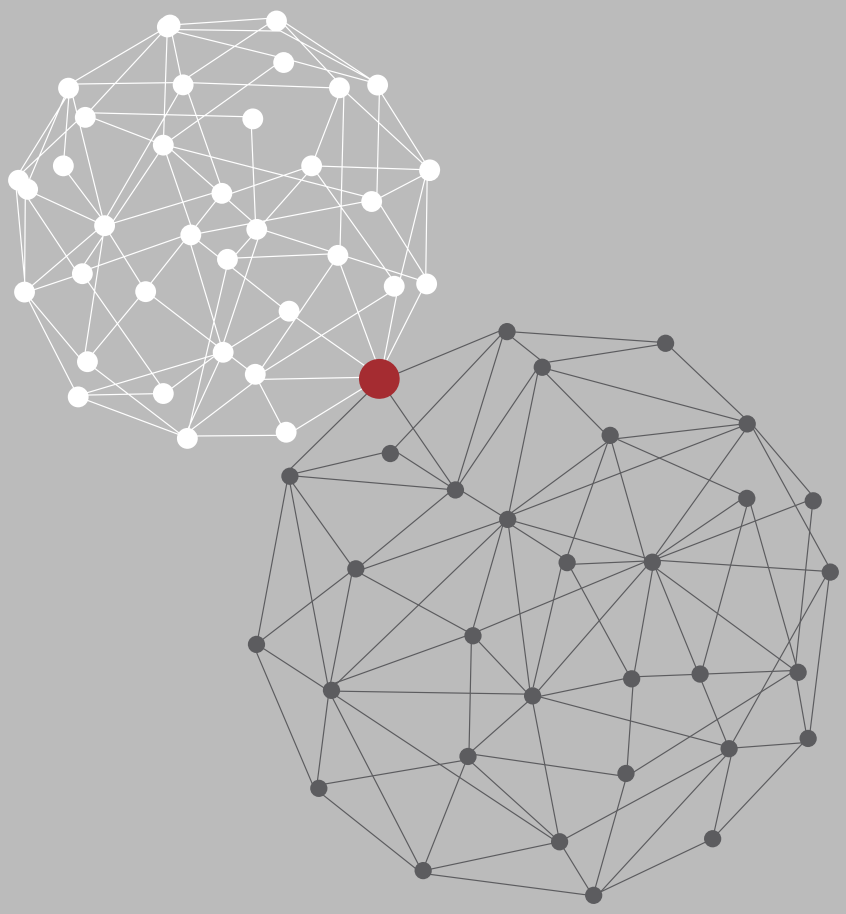
From Phantom to Patient



MADELEINE KOK

Individual Optimisation of Contrast Media Application and Radiation Dose in Computed Tomographic Angiography;

From Phantom to Patient

PROEFSCHRIFT

Ter verkrijging van de graad van doctor
aan de Universiteit Maastricht,
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CHAPTER 1
General introduction

COMPUTED TOMOGRAPHIC ANGIOGRAPHY

Computed tomographic angiography (CTA) is an imaging method which is widely used as a diagnostic tool for the visualisation and evaluation of vascular structures such as carotid arteries, the circle of Willis, pulmonary arteries, coronary arteries, the thoracic and abdominal aorta as well as peripheral arteries.
CTA technology has undergone many changes in the past two decades; especially the advent of multidetector-row CT (MDCT) with high spatial and temporal resolution, wider detector coverage, increased rotation speed and iterative reconstruction (IR) improved image quality, resulting in improved visualisation of these various vascular structures.[1-10]

IMAGE QUALITY

Reasonable image quality is the prerequisite for optimal diagnostic accuracy. Image quality of a CTA depends on a combination of the degree of intravascular enhancement, image noise and the presence of artefacts. Even with technical advances of MDCT, image quality is still subject to changes by aforementioned factors since they are influenced by different parameters: contrast media (CM) characteristics, injection parameters, scan technique and patient related factors.[11-14] **Figure 1.1** shows the different factors influencing image quality in CTA.

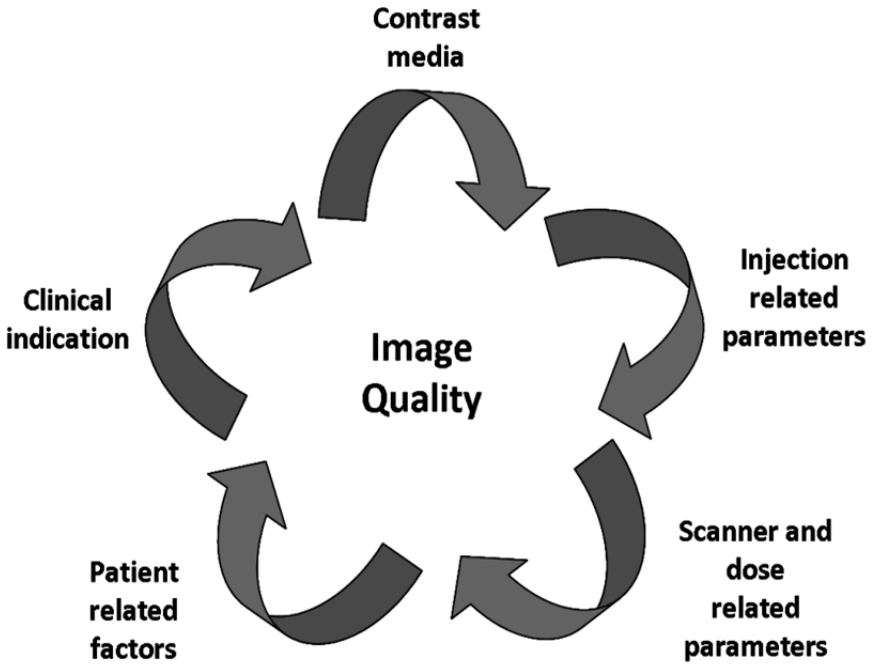

Figure 1.1 influencing factors on image quality for CTA

CM AND INJECTION RELATED FACTORS

Previous studies have already investigated the influence of iodine concentration, injection rates and iodine delivery rate (IDR) on diagnostic intravascular enhancement.[15-22] The influence of the iodine concentration on arterial enhancement has led to contradictory statements in the literature. In coronary arteries, publications have mainly stated that the use of higher concentrated CM significantly increases arterial attenuation compared to the use of lower CM concentrations.[21, 23] However, the IDR and total iodine load (TIL) in those studies were variable. In turn, other studies showed that the use of low and high CM concentrations will result in comparable arterial enhancement, when using an identical IDR and TIL.[20, 22]

Another important CM characteristic is viscosity – as the viscosity of CM is relatively high and consequently increases the viscosity of blood plasma.[24]
Viscosity plays an important role in CM delivery, as viscosity is directly influenced by temperature, meaning viscosity decreases with increasing temperature.[16, 25-27] On the other hand, viscosity increases with higher iodine concentration of CM. Low viscosity

could be beneficial in terms of lower injection pressure and therefore higher injection rates might be accepted.
Higher injection rates, in turn, might be advantageous in CTA if high intravascular enhancement is required. This can be achieved by higher IDR – defined as the factor of flow rate and CM concentration [gI/s].[12, 22] A high IDR can be achieved by using either a standard concentrated CM at a relatively high injection rate or a highly concentrated CM at a lower injection rate.

SCAN RELATED FACTORS

The scan protocol also has an influence on image quality; scan parameters influence intravascular enhancement, image noise and the presence of artefacts. For example, lowering tube voltage [kVp] in CTA increases the degree of vascular contrast enhancement.[28-30] This is explained by the fact that lower tube voltage translates into lower effective photon energy (effective photon energy being approximately half the kVp), bringing the latter closer to the K-edge of Iodine (33.2keV).[31, 32] Higher intravascular enhancement may increase the signal-to-noise ratio (SNR) since image noise remains constant at normalised dose settings. However, if lower tube voltages are used without concordantly increasing tube-current-time product settings [mAs], the reduced radiation dose exposure will result in increased image noise and invariably the SNR will decrease. Therefore, selecting scan parameters such as tube voltage and tube-current-time product can be very complex and must be adjusted to the clinical indication as well as to the patient's anatomy.
In addition, new reconstruction technologies such as IR reduce image noise and improve image quality in comparison to routinely used filtered back projection (FBP)[33-36], which may help to maintain diagnostic image quality whilst using reduced radiation dose.

PATIENT RELATED FACTORS

With respect to patient's anatomy, the level of intravascular enhancement decreases with increased body weight due to increased circulating blood volume and cardiac output. This correlation was found to be clinically significant, as well as the correlation between intravascular enhancement and body mass index (BMI).[12, 37] Higher body weight also significantly decreases SNR compared to lower body weight, due to the fact that there is more absorbing tissue in the scan range.[30] In obese patients, body surface area [$kg^{0.65}$][38] and lean body weight (weight other than fat) should also be considered, as these patients have a high proportion of body fat and a relatively small blood volume and proportionally a small well-perfused extracellular compartment.[12]

Furthermore, the presence of prosthesis materials or stent-grafts in patients will more frequently result in artefacts when lower kVp settings are used.

CLINICAL INDICATION

Several above described factors are determined by the clinical indication for CTA. For example, different vascular structures will be imaged using a particular scan acquisition protocol resulting in specific scan duration. Logically, the scan duration may influence the injection time and injection parameters need to be adapted accordingly. Nowadays it is possible to perform a coronary CTA (CCTA) or CT pulmonary angiography (CTPA) in 1 – 2 seconds only. This requires sharp bolus timing and a smaller CM bolus might be feasible. On the other hand, performing CTA of the entire aorta or even combined CTA acquisitions (e.g. coronary arteries + entire aorta) will increase the scan duration making optimal bolus timing at each level more challenging; a longer injection duration is required to ensure that the CM bolus will not run out during the scan.
A different minimum degree of intravascular enhancement is required for each vascular structure. For example, the required enhancement for pulmonary arteries is about 180 Hounsfield Units [HU][39], whereas the required degree for the aorta and coronary arteries is 200-250HU[40, 41] and 325HU, respectively.[42] Thus, the optimal intravascular enhancement degree is related to the particular vascular structure and the underlying clinical indication.
Furthermore, various clinical indications also include diversity in differential diagnosis within the same vascular structure. For example, in patients referred for transcatheter aortic valve implantation (TAVI), a CTA aorta will be performed and optimal image quality – meaning high enhancement and low image noise – is required at the level of the ascending aorta only, in order to ensure adequate assessment of aortic root dimensions for different time points within the cardiac cycle. For the evaluation of peripheral access higher noise levels are acceptable as treatment requires information regarding vessel diameters and extent of calcifications. For other indications of CTA aorta; bleeding, dissection or stenosis of the smaller branches such as the renal arteries, low image noise levels are recommended.

DRAWBACKS FOR CTA

Although CTA has some advantages over other image modalities, there are also potential drawbacks for CTA. These potential drawbacks include the administration of iodinated CM – which may cause allergic reactions or contrast induced nephropathy (CIN). Previous investigation found that CIN occurs in >10% of patients who undergo contrast enhanced CT in the outpatient setting and is associated with a significant risk

for severe renal failure and death.[44] In this respect, contrast volume has been identified as most important risk factor on CIN.[43, 44]
Furthermore, the use of ionising radiation dose can lead to induction of point mutations, chromosomal translocations, and gene fusions, which are all linked to the induction of cancer. Although the individual risk estimates are small, the concern about the risks from CT is mostly related to the rapid increase in its use. On the basis of risk on CT use from 1991 through 1996, it has been estimated that about 0.4% of all cancers in the United States may be attributable to the radiation from CT studies. By adjusting the estimate ten years later, this estimate was increased four to five times already.[46] Therefore, the reduction of radiation exposure to the patient during CT is one of the most important requirements of the as low as reasonably achievable (ALARA) principle.[45-48]

OUTLINE OF THE THESIS

CTA is widely used as a diagnostic tool for different vascular diseases. With the advances in knowledge on all above stated self-contained factors influencing image quality of CTA, the most challenging part is to efficiently combine these factors in order to ensure optimal image quality while providing the opportunity to reduce radiation dose and CM volume. Therefore, we attempted to individually adapt injection and scan parameters in CTA for different clinical indications.

Chapter 2 provides insight in the relationship between different CM characteristics, namely CM concentration and viscosity. In addition, the influence of viscosity on injection parameters – and especially injection pressure – during coronary CTA was investigated using a circulation phantom.

Chapter 3 explores the relationship between CM characteristics, injection parameters, radiation dose and image quality in general CTA using a circulation phantom. The potential for automated kVp-selection to reduce the radiation dose during CTA using different concentrated CM – normalised to an identical IDR – was evaluated.

Chapter 4 investigates how scan parameters – especially kVp settings – influence the intravascular enhancement in CTA. A circulation phantom was used to systematically investigate how IDR and CM volume can be adapted to a particular kVp setting in order to obtain optimal enhancement levels. Based on these primary results, the concept was clinically tested in sixty patients referred for CCTA.

Chapter 5 studies the effect on image quality when using body weight adapted injections in patients referred for CTPA. The benefits of individualised CM protocols for patients of different body sizes were investigated. We hypothesised that the use of a standard CM protocol with fixed parameters could more often result in enhancement levels below diagnostic level for heavier patients, whereas these enhancement levels may be higher than required for smaller patients.

Chapter 6 elaborates on the role of individual adaptation of both injection and scan protocols in patients referred for pre-TAVI CT examination. These patients frequently suffer from an impaired renal function, which enhances the importance of CM reduction. However, in order to ensure technical success and optimal valve-prosthesis sizing, dedicated scan technique including reliable CM injection protocols are of utmost importance providing optimal filling at the level of the aortic root as well as the peripheral arteries. Our purpose was to evaluate the possibility of reducing CM volumes while using lower kVp settings in combination with IR.

Chapter 7 studies the possibility of reducing radiation dose exposure and CM volume in patients referred for the standard evaluation of the aorta, without compromising image quality. Aortic CTA is associated with frequent follow-up over time, which implies high cumulative radiation dose and iodinated CM volumes for these patients. Therefore, we investigated the effect on radiation dose exposure and CM volume of individualised scan and injection protocols and compared these to current protocols using fixed parameters.

Chapter 8 contains the general discussion on the relationship between all factors influencing image quality in CTA as mentioned by all above stated manuscripts, as well as future perspectives on this topic.

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CHAPTER 2

Influence of contrast media on viscosity and temperature on injection pressure in computed tomographic angiography: a phantom study.

Kok M, Mihl C, Mingels AM, Kietselaer BLJH, Mühlenbruch G, Seehofnerova A, Wildberger JE, Das M.
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ABSTRACT

Purpose

Iodinated contrast media (CM) in CT angiography (CTA) is characterised by its concentration and consecutively by its viscosity. Viscosity itself is directly influenced by temperature, which will furthermore have an impact on injection pressure. Therefore, the purpose of this study was to systematically evaluate the viscosity of different CM at different temperatures and to assess their impact on injection pressure in a circulation phantom.

Methods and materials

Initially viscosity of different contrast media concentrations (240, 300, 370 and 400mgI/ml) was measured at different temperatures (20°C-40°C) with a commercially available viscosimeter. In the next step a circulation phantom with physical conditions was used. Contrast media was prepared at different temperatures (20°C, 30°C, 37°C) and injected through a standard 18G needle. All other relevant parameters were kept constant (iodine delivery rate IDR=1.9gI/s: total amount of iodine=15gI). Peak flow rate [ml/s] and injection pressure [psi] were monitored. Significance differences were tested by the Kruskal-Wallis test (SPSS).

Results

Viscosities for iodinated CM of 240, 300, 370 and 400mgI/ml at 20°C were 5.1, 9.1, 21.2, and 28.8mPa.s, respectively, while at 40°C these were substantially lower (2.8, 4.4, 8.7, and 11.2mPa.s). In the circulation phantom, peak pressures (mean±SD) for CM 240mgI/ml at 20°C, 30°C, and 37°C were 107±1.5, 95±0.6, 92±2.1psi; CM 300mgI/ml: 119±1.5, 104±0.6, 100±3.6psi; CM 370mgI/ml 150±0.6, 133±4.4, 120±3.5psi; and CM 400mgI/ml 169±1.0, 140±2.1, 135±2.9psi respectively, with all p-values <0.05.

Conclusion

Low concentration, low viscosity and high temperatures of CM are beneficial in terms of injection pressure. This should also be considered for individual tailored contrast protocols in daily routine scanning.

INTRODUCTION

The quality of computed tomography angiography (CTA) and especially coronary computed tomography angiography (CCTA) depends utmost on the degree of intravascular enhancement. Sufficient vessel attenuation is crucial for proper evaluation of vascular pathology, especially with respect to smaller vessels.[1] Enhancement characteristics are influenced by scan technique, patient related factors, contrast media (CM) characteristics as well as injection parameters.[2-5] Previous studies already investigated the influence of iodine concentration, injection rates and iodine delivery rate (IDR) on diagnostic intravascular attenuation.[1, 6-12]

Another factor that plays an important role in CM delivery and thus enhancement is viscosity. Viscosity is directly influenced by temperature, which means viscosity decreases with increasing temperature.[7, 13-16]

On the other hand, viscosity of CM increases with higher iodine concentrations. Low viscosity will be advantageous in several ways: Injection pressure is lower and CM distribution in the blood might be facilitated. This can potentially be advantageous for the visualisation of distal vessel segments.[2, 6] However, this comes at the expenditure of higher flow rates when an identical IDR has to be maintained. Only few studies investigated differences in injection pressure with different injection protocols.[1, 17]

Literature about CM characteristics and injection parameters remains heterogeneous and controversial. Intravascular attenuation will not significantly change with iodine concentration in a standardised setting.[11] Thus, the purpose of this study was to evaluate different CM with different iodine concentrations in a standardised manner at different temperatures and to further investigate its influence on injection parameters, with special regard to injection pressure.

METHODS AND MATERIALS

Viscosity analysis

Viscosity was measured in a standard lab environment as depicted in **figure 2.1**, using a commercially available viscosimeter (Ostwald viscosimeter; Julabo GmbH, Seelbach, Germany). Monomeric non-ionic and low-osmolar CM were used (iopromide 240, 300, 370 [Ultravist; Bayer Healthcare, Berlin, Germany] and iomeprol 400 [Iomeron; Bracco Imaging, Milan, Italy]) containing 240, 300, 370, and 400mgI/ml, respectively. CM was warmed up in a standardised and controllable fashion in a water bath, which was immediately followed by loading the u-tube of the viscosimeter with 2ml CM. The measurements were performed between 20˚C and 40˚C with steps of two degrees centigrade. All measurements were repeated two times to determine reproducibility.

Kinematic viscosity [mm^2/s] was defined by multiplying the constant of the u-tube with the exact time that was required for each CM to run through the u-tube. Dynamic viscosity [mPa.s] was defined by multiplying the kinematic viscosity [mm^2/s] with the corresponding density of CM [gI/ml]. Density of CM [gI/ml] was measured using a commercially available density instrument (Mettler Toledo Densito 30PX, Columbus, OH, USA).

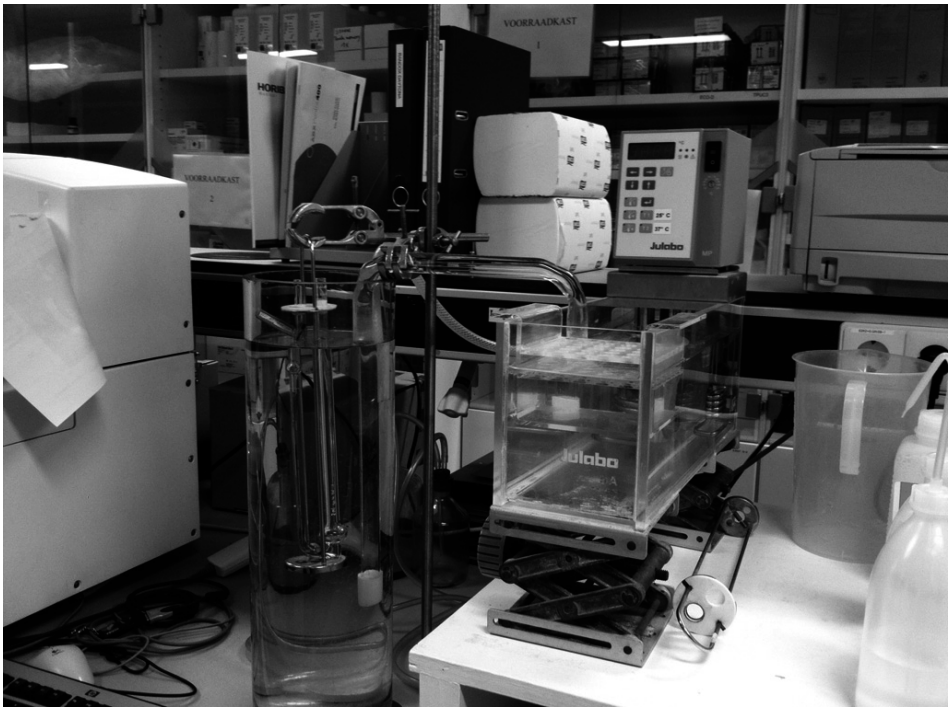

Figure 2.1 The U-tube of the viscosimeter
Left: U-tube hanging in the water bath, which is connected with a tube to the main water bath with temperature control *(right)*

Circulation phantom

A modified circulation phantom with physiological circulation parameters was used as first described by Behrendt *et al.*[18] This phantom consists of a low-pressure lung and a high-pressure body circulation system, with accurate replicas of the entire aorta, as well as the coronary arteries (**figure 2.2**). In addition, the phantom consists of connecting tubes, a water filled acrylic container, two pressure meters and a pressure relieve valve for modulation of arterial and venous pressure. The phantom was filled with water at body temperature (37˚C), and subsequently circulation was driven by a pulsa-

tile Harvard medical heart pump (BS4, Harvard Apparatus, Holliston, MA). All values were set within physiological limits: heart rate 60 beats per minute [bpm]; stroke volume 60ml; diastole/systole ratio 60:40 and blood pressure 120/80mmHg. Both aortic and coronary elements of the phantom were encased in a water-filled acrylic container, mimicking CT-attenuation characteristics of the mediastinum. The phantom was connected to the scanner's electrocardiogram (ECG) lead inputs, in order to provide a synchronised ECG waveform based on the phantom's parameters.

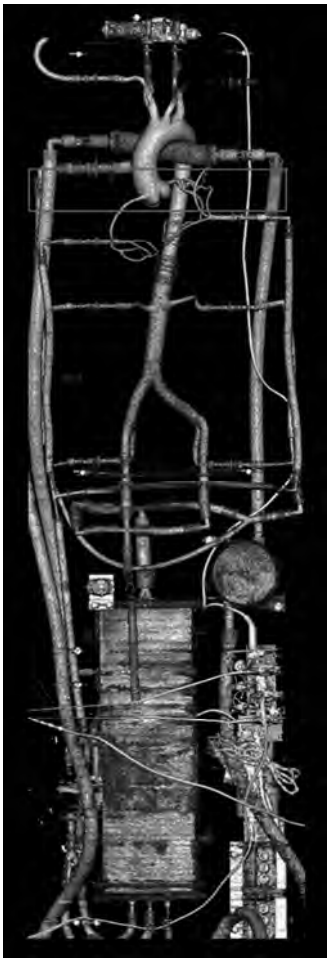

Figure 2.2 Three-dimensional reconstruction of the circulation phantom with scan range outlined

CM concentration [mgI/ml]	CM Volume [ml]	CM flow rate [ml/s]	IDR [gI/s]	Total amount of iodine [gI]	Injection time [s]
240	62.5	7.9	1.9	15.0	7.9
300	50	6.3	1.9	15.0	7.9
370	40.5	5.1	1.9	15.0	7.9
400	38	4.8	1.9	15.0	7.9

Table 2.1 Injection parameters for all CM protocols

Injection and scan protocol

CM with consecutive iodine concentrations of 240mgI/ml, 300mgI/ml, 370mgI/ml and 400mgI/ml was injected with different pre-heated temperatures (20˚C, 30˚C and 37˚C). IDR and total amount of iodine in all groups were kept identical (1.9gI/s and 15gI, respectively). Flow rates and applied contrast media injection protocols used are listed in **table 2.1**. After every scan, the phantom was flushed with water from the container. CM was injected into the phantom using a standard CT power injector (Stellant, MEDRAD, Pittsburgh, USA), through a three-way stopcock extension tube and a standard 18G needle (Sterican, Braun, Melsungen, Germany), into the injection port (**figure 2.3**). Injection time was set to 7.9s for all injections throughout the experiment, no saline chaser was used.

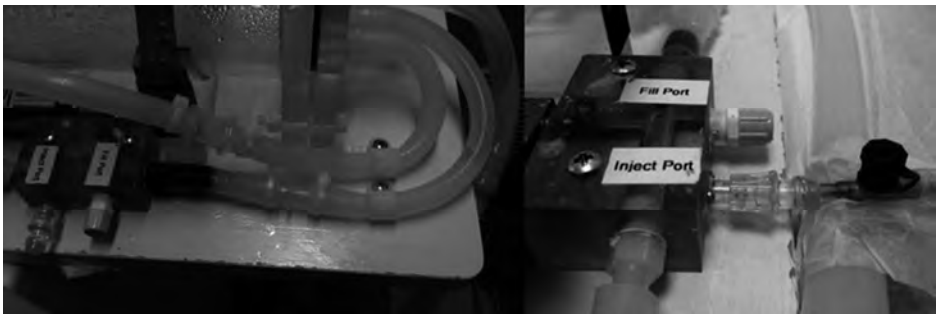

Figure 2.3 Injection port of the circulation phantom
Left: injection port connected to a tube that enters the circulation phantom. *Right*, close-up: 18G needle connected to the CM injector and inserted in the injection port of the phantom

Temperature of the pre-heated CM was measured prior to scanning. All relevant injection related parameters as total amount of CM used, flow rate, peak flow rate and peak pressure were closely monitored using the Certegra^{TM} Informatics Platform (Bayer-Medrad, Indianola, PA). In addition, an independent data acquisition system (National Instruments Corporation, Austin, TX) was used to monitor the physiological parameters of the phantom throughout the experiments.
Serial CT-scans were performed at the level of the ascending aorta (AA), descending aorta (DA) and the coronary arteries (at the level of the left main coronary artery [LM]), using a 2nd generation DSCT scanner (Definition Flash, Siemens Healthcare, Forchheim, Germany) with a sequential examination protocol (2x64x0.6mm slice collimation, tube voltage of 120kVp, 150mAs$_{eff}$, at a gantry rotation time of 500ms, a cycle time of 1000ms). Reconstruction was performed with an adapted field of view (FOV) at 5mm thick sections using a soft reconstruction kernel (Siemens B30f). All protocols were repeated three times each to determine reproducibility.

Quantitative analysis

All injection related parameters were read out after each injection.
Peak attenuation was measured on all serial CT-scan images by delineating a circular region of interest (ROI) in the AA, DA and LM (**figure 2.4**). A constant maximum size of intra-luminal ROI was set and maintained at all anatomic sites. Resulting average attenuation values for each CM protocol were compared graphically using time-enhancement curves for all vessels. All measurements were independently analysed by two experienced observers, blinded to each other's results. Peak enhancement and time to peak (TTP) were determined for all vessels.

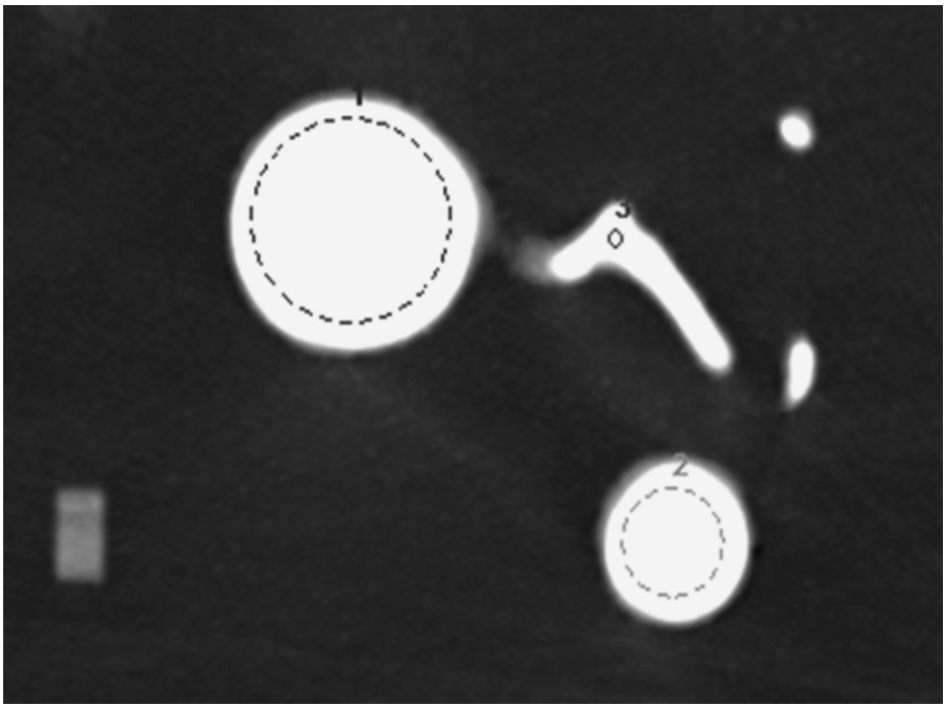

Figure 2.4 Measurement performances on images of the serial CT scans
Mean attenuation was measured by placing a circular ROI in the AA (1), DA (2), and the LM (3)

Statistical analysis

Peak pressures in different concentrations CM and different temperatures were compared using the non-parametric Kruskal-Wallis one-way analysis of variance by ranks. Also TTP and attenuation values in both AA and DA as well as the LM were compared using the non-parametric Kruskal-Wallis one-way analysis of variance by ranks. In addition, attenuation values of AA, DA and LM in all contrast media groups were compared individually by means of independent samples T-test. The values are expressed as the mean ± standard deviation (SD). Interobserver agreement was calculated using the intraclass correlation coefficient in a two-way mixed effects model. Data analysis was conducted with SPSS version 20.0 (SPSS Inc, Chicago, IL). All p-values are 2-sided, and a p-value below 0.05 was considered statistically significant.

RESULTS

The exact time required for each CM to run through the u-tube was measured twice and varied between 213s (for 240mg/ml in 40˚C) and 1740s (for 400mg/ml in 20˚C). The average of two measurements was used to calculate the viscosity, because of the high reproducibility of the experiments (difference between times was max. 1s). The viscosity values for iodinated CM of 240, 300, 370, and 400mgI/ml as measured with the viscosimeter between 20˚C and 40˚C in the laboratory are given in **table 2.2** and **figure 2.5**. The lowest viscosity was found for the lowest concentrated CM of 240mgI/ml at the highest temperature (2.8mPa.s at 40˚C). The highest viscosity was found at room temperature for the highest concentrated CM of 400mgI/ml (28.8mPa.s at 20˚C). At body temperature, the viscosity of highest concentrated CM (400mgI/ml; 12.6mPa.s at 37˚C) is still higher than CM of 300mgI/ml at room temperature (9.1mPa.s at 20˚C).

Temperature [˚C]	Iopromide [240mgI/ml]	Iopromide [300mg I/ml]	Iopromide [370mg I/ml]	Iomeprol [400mg I/ml]
20	5.1	9.1	21.2	28.8
21	4.9	8.7	19.7	27.2
23	4.6	8.0	17.8	24.1
25	4.3	7.3	16.0	22.2
27	4.0	6.8	14.2	20.1
29	3.7	6.3	13.0	18.3
31	3.5	6.0	12.0	16.4
33	3.4	5.6	11.1	15.0
35	3.2	5.2	10.2	13.7
37	3.1	4.9	9.8	12.6
38	3.0	4.7	9.4	12.1
39	2.9	4.6	9.0	11.6
40	2.8	4.4	8.7	11.2

Table 2.2 Viscosity levels of different iodine concentrations at different temperatures
Viscosity levels are expressed in mPa.s

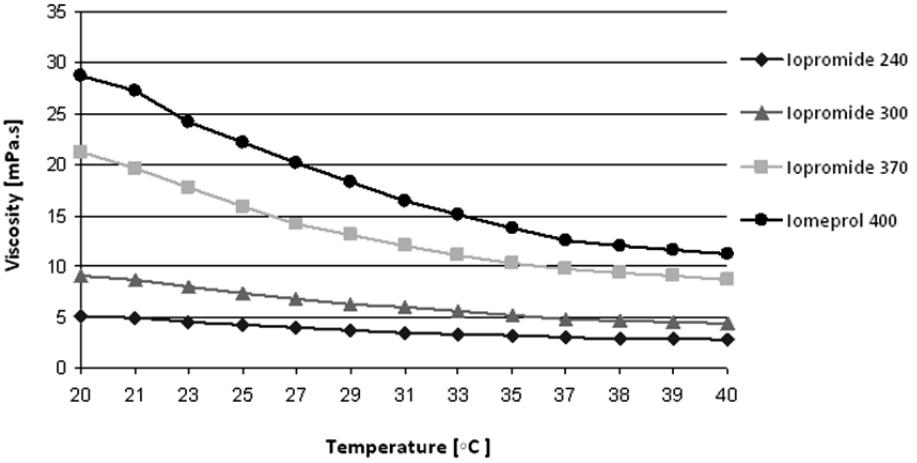

Figure 2.5 Graph lines showing the effect of different temperatures on the viscosity of iodinated CM with different iodine concentrations

The effect of temperature and iodine concentration was further validated in the circulation phantom. No pressure or circulation related problems were encountered throughout the experiments.

Table 2.3 shows that significant differences in peak pressure [psi] were found at 20˚C, 30˚C, and 37˚C for iodinated CM 240, 300, 370, and 400mgI/ml. **Figures 2.6 and 2.7** furthermore show that significant differences in peak pressure [psi] were found between all different CM. Overall, the lowest peak pressure was found for the lowest concentrated CM of 240mgI/ml at body temperature (92psi at 37˚C).

CM [mgI/ml]	Mean peak pressure [psi] 20˚C	Mean peak pressure [psi] 30˚C	Mean peak pressure [psi] 37˚C	*p*-value
240	107±1.5	95±0.6	92±2.1	0.027
300	119±1.5	104±0.6	100±3.6	0.027
370	150±0.6	133±4.4	120±3.5	0.026
400	169±1.0	140±2.1	135±2.9	0.027
p-value	0.015	0.017	0.015	

Table 2.3 Mean peak pressure in different iodine concentrations of CM and temperatures
P-values < 0.05 were considered to be statistically significant

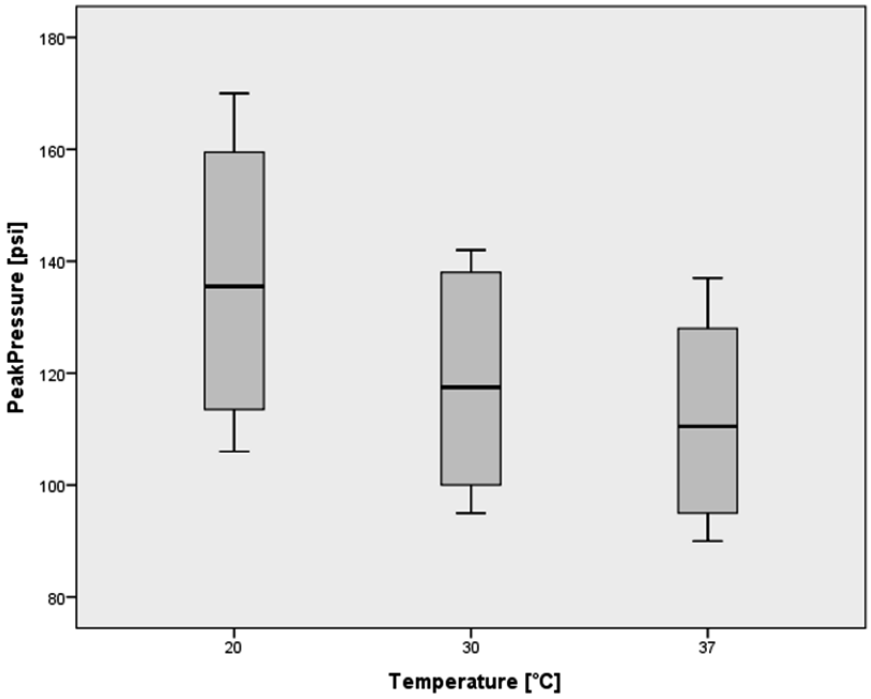

Figure 2.6 Pooled box plots showing different temperatures on the x axis and peak pressure values for the tested CM concentrations on the y axis
The horizontal line is the median, the ends of the box are the upper and lower quartiles, and the vertical lines are the full range of values in the data

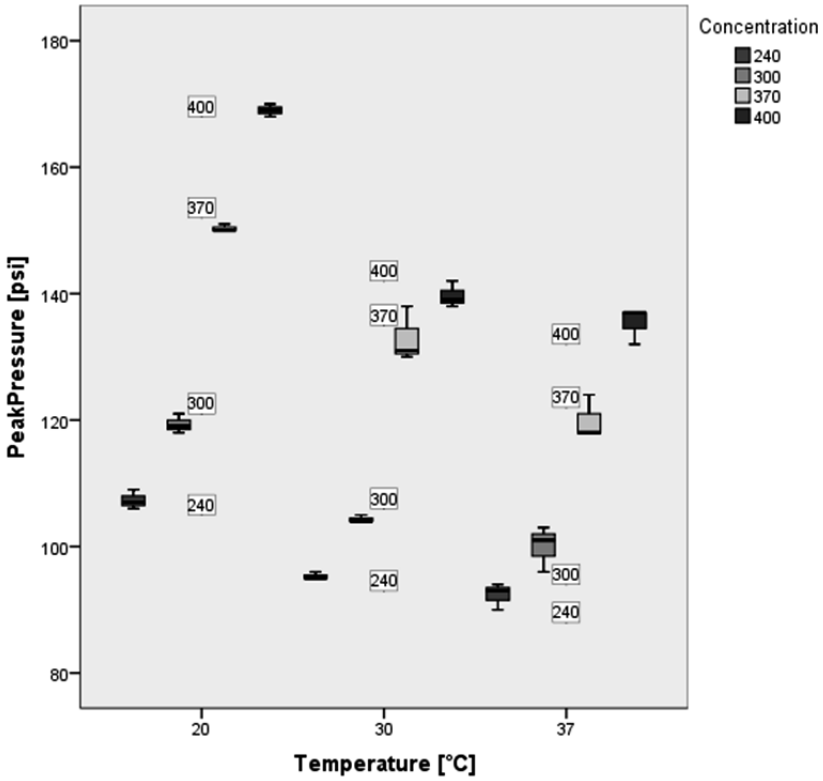

Figure 2.7 Detailed box plots showing different temperatures on the x axis and peak pressure values in different concentrations CM on the y axis
These box plots are clustered by the concentration of CM

No significant differences could be detected in TTP [s] for AA, DA and LM, respectively as can be seen in **table 2.4**. Consecutively mean peak attenuation values were comparable and not statistically different for all protocols at different temperatures and with different iodine concentrations (**table 2.5**). The reproducibility of the attenuation values proved to be very good: inter-observer correlation was high (>0.910).

CM [mgI/ml]	TTP AA [s]			TTP DA [s]			TTP LM [s]		
	20◦C	30◦C	37◦C	20◦C	30◦C	37◦C	20◦C	30◦C	37◦C
240	10.4±0.5	11.0±0.0	10.0±0.0	12.1±0.1	12.7±0.6	12.1±1.1	10.7±0.5	11.0±0.0	10.7±0.6
300	10.1±0.9	10.3±0.6	10.7±0.6	11.7±0.5	12.0±0.0	12.1±0.1	10.1±0.9	10.3±0.6	11.1±0.1
370	10.7±0.6	11.8±0.7	11.1±0.1	12.4±0.5	13.8±0.7	13.1±0.1	11.1±1.1	11.8±0.5	10.7±1.1
400	11.3±0.6	12.0±0.0	11.5±0.5	13.4±0.5	13.7±0.6	13.1±0.1	11.4±1.2	11.7±0.6	12.5±1.1
p-value	0.595	0.445	0.155	0.179	0.216	0.287	0.577	0.167	0.120

Table 2.4 Mean time to peak in the ascending aorta (AA), the descending aorta (DA) and the left main coronary artery (LM)
P-values < 0.05 were considered to be statistically significant

CM [mgI/ml]	AA [HU]			DA [HU]			LM [HU]		
	20◦C	30◦C	37◦C	20◦C	30◦C	37◦C	20◦C	30◦C	37◦C
240	424±10	419±2	418±6	418±3	412±5	414±4	418±2	419±6	417±2
300	429±8	420±6	420±5	427±4	413±4	416±5	414±6	410±6	407±2
370	424±5	420±8	430±7	417±5	416±4	423±9	417±10	412±10	422±10
400	433±27	426±4	432±8	417±27	422±17	425±5	417±20	427±10	417±14
p-value	0.680	0.275	0.172	0.259	0.742	0.170	0.889	0.141	0.213

Table 2.5 Mean peak attenuation values in the ascending aorta (AA), the descending aorta (DA) and the left main coronary artery (LM)
Values are expressed as mean±SD. P-values < 0.05 were considered to be statistically significant

DISCUSSION

Different CM have different characteristics mainly due to their amount of iodine. Viscosity is directly correlated to the amount of iodine per milliliter. This was confirmed with our experiments as it was shown that highest concentrated CM (400mgI/ml) was associated with the highest viscosity of the CMs studied. Interestingly, even under optimal conditions (at body temperature of 37°C), highest concentrated CM had a higher viscosity as e.g. 300mgI/ml at room temperature.
Viscosity itself plays an important role in CM delivery and enhancement.[3, 19, 20] Cademartiri *et al*[7] stated that preheating CM (400mgI/ml) from 20°C to 37°C decreases the viscosity by more than 50% (27.5 to 12.6mPa.s), as confirmed in our study.
Knollmann *et al*[17] showed that high iodinated CM (370mgI/ml and 400mgI/ml) reached the pressure limit at certain high injection rates and concluded that these were problematic due to their high viscosity.

Low viscosity should reduce injection pressure and may accelerate CM distribution within the blood.[3, 6] Until now, several studies focused on optimisation of intravascular contrast enhancement and in particular on the influence of injection rate, iodine concentration and IDR, respectively.[2, 8, 9, 21-25] But none of these studies systematically investigated the effect of pre-heated CM on intravascular enhancement or on these injection parameters. Schwab *et al*[15, 16] concluded that heating CM (300mgI/ml) effectively reduces injection pressure, when tested with injection cannulas of different sizes.
Significant differences in peak pressure were found for all concentrations at different temperatures. The other way around, significant differences in peak pressure were found for all temperatures in the different concentration groups. Highest efficacy of reduced viscosity by preheating CM (from 20°C to 37°C) was found for highest concentrated CM (400mgI/ml): 56% reduced viscosity compared to 41% reduced viscosity in 240mgI/ml, the peak pressure for the highest concentrated CM (400mgI/ml) was even higher at body temperature (135psi at 37°C) when compared to CM with 240 at room temperature (107psi at 20°C). Given the statistical significance of these findings, the positive effect of preheating CM in order to reduce viscosity and therefore, to reduce injection pressure, is stressed.
Furthermore, low viscosity should allow an accelerated distribution within the blood and thus potentially better visualisation of small sized vessels and for advanced perfusion protocols. This could potentially be helpful in the assessment of tumor patients as dedicated workup on blood flow, time to peak and blood volume as a marker of angiogenesis.[26]
Last but not least, attenuation levels were comparable for all CM, which again underlines the fact, that IDR is the most important parameter when different CM are compared. The results of our study will have major implications for the logistical work-up

within a CT suite. For instance, incubators and heating cabinets will allow standardised pre-heating of CM to the desired temperature Furthermore, if not single vials and disposables are used for a single patient, CM temperature has to be maintained after the CM bottles are taken out and are opened up. This can be guaranteed by using dedicated injection power injectors or other preheating devices at the scanner site (**figure 2.8**).

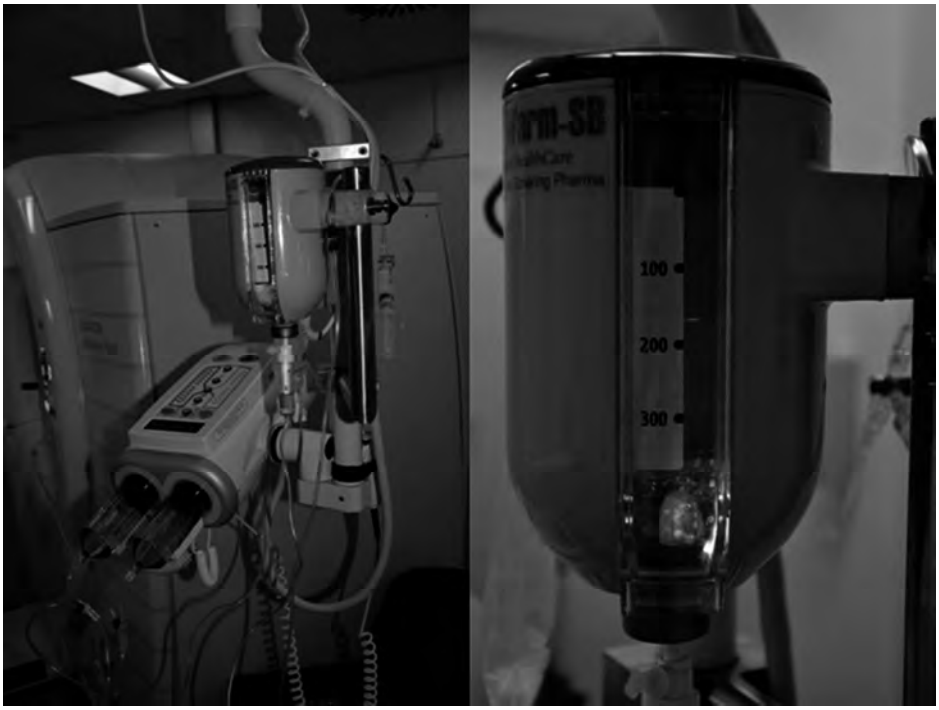

Figure 2.8 Photograph of the pre-heating device next to the CT scanner
WARM-SB (Nemoto International, Herent, Belgium) facilititates constant temperature, even if the bottle is opened up. The maximum bottle volume for this setup is 500ml

Limitations

Pre-heating CM and precise registering of temperature before injection is mandatory in this phantom study to evaluate the influence of viscosity on these parameters. In this experiment, pre-heated CM in bottles of 100ml was used. Scanning was commenced, directly after measurement of the temperature, in order to keep temperatures constant. However, the preheated CM was used in two or three repetitive scans. The possibility exists that temperature will decrease within small margins and with that viscosity could have increased after several minutes. However, injection parameters such as peak flow rate and peak pressure did not differ significantly from each other.

CONCLUSION

The results of these experiments show in a standardised way that high temperature, low concentration iodine and low viscosity decrease injection pressure. This impacts individual tailored contrast protocols in daily routine scanning. Standardised pre-heating should be a prerequisite for clinical CM administration.

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CHAPTER 3

Automated kVp selection for radiation dose reduction in CTA – is it independent from contrast media concentration?

Kok M, Mihl C, Seehofnerova A, Turek J, Jost G, Haberland U, Wildberger JE, Das M.
AJR Am J Roentgenol. 2015 Dec;205(6):1332-8.

ABSTRACT

Purpose

The purpose was to systematically investigate radiation dose reduction using automated tube voltage [kVp] selection during CTA and to evaluate the impact of contrast media (CM) injection protocols on dose reduction.

Materials and methods

A circulation phantom containing the thoracic-abdominal vasculature was used. Four different CM concentrations (iopromide 300 and 370mgI/ml and iomeprol 350 and 400mgI/ml) were administered, maintaining an identical iodine delivery rate (1.8gI/s) and total iodine load (20gI). Three different scan protocols for CTA of the thoraco-abdominal aorta were used: A: no dose modulation; B: automated tube current modulation (CAREDose4D^{TM}); and C: automated tube voltage selection (CAREkV^{TM}). The dose-length product was recorded to calculate the effective dose. Attenuation values [HU], image noise levels and signal-to-noise ratios in six predefined intravascular sites (3 thoracic and 3 abdominal) were measured by two readers. All values were analysed using the Kruskal-Wallis test and two-way ANOVA.

Results

There was a significant reduction in the effective dose [mSv] for protocols B (2.03±0.1mSv) and C (1.00±0.0mSv) compared to protocol A (4.34±0.0mSv). The dose was reduced by 53% for protocol B and by 77% for protocol C. No significant differences were found in the effective dose between the different CM injection protocols within the scan protocols; all *p*-values >0.05. The attenuation values and signal-to-noise ratios were comparable between all different CM injection protocols; all *p*-values >0.05.

Conclusion

A large radiation dose reduction (77%) can be achieved using automated tube voltage selection, independent of the CM injection protocols.

INTRODUCTION

The reduction of radiation exposure to the patient during computed tomography (CT) studies is one of the most important requirements of the as low as reasonably achievable (ALARA) principle.[1-4] Different methods of reducing the radiation dose have been developed in recent years. Aside from low-dose protocols using a reduced tube current that is adjusted to the patient's size, automated attenuation-based tube current modulation and kVp selection[2, 5-9], high-pitch scanning[10-12] and iterative reconstruction[13] have been evaluated in several studies.

Automated tube current [mAs] modulation is widely used in clinical settings and is based on the principle that X-ray attenuation and quantum image noise are determined by the size of the object and its tissue density.[14]

Furthermore, the tube voltage [kVp] displays a strong potential for radiation dose reduction due to the use of lower tube voltages (dose reduced by approximately the square root of the tube voltage).[15-19] In contrast enhanced CT angiography (CTA), the potential for a reduction of the radiation dose is particularly high. The x-ray attenuation of iodine is significantly higher at lower tube voltages (low-energy x-rays are better absorbed by iodine).[20] However, the use of a lower kVp affects not only the radiation dose and contrast but also the image noise.[21] Therefore, the tube current must be adjusted to the tube voltage, the diagnostic task and the patient's anatomy. Automated kVp-selection is performed using a software tool that uses information gathered by the topogram and user-defined reference values to optimise the tube current and voltage for the diagnostic objective. Thus, the algorithm calculates the x-ray tube settings using the lowest radiation dose required for the user-defined image quality. The full potential of this method can be achieved using the latest technology, high-power x-ray tubes, enabling the effective use of lower tube voltages, even for larger objects.[22]

The use of lower tube voltages leads to an obviously higher contrast media (CM) signal enhancement and in turn allows an increase of image noise and hence reducing the radiation dose while maintaining the signal-to noise ratio (SNR). This effect is especially effective in CTA, in which the attenuation is primarily based on the vessel CM opacification. However, the intravascular SNR does not exclusively depend on the technical imaging parameters. The basis of the attenuation, i.e., the intravascular iodine concentration, primarily depends on the contrast injection protocol. For CTA, the key contrast parameters are the CM concentration, the injection rate and, consequently, the iodine delivery rate (IDR; [gI/s]). A high IDR that is required for CTA can be achieved by using a standard concentrated CM at a relatively high injection rate or a highly concentrated CM at a relatively low injection rate.

Aside from the iodine concentration, different CM also display distinct physicochemical properties, such as the increase in the osmolarity and the viscosity with increasing iodine concentration. In particular, increased viscosity affects the vascular flow, which, in turn, may alter the shape of the bolus profile[23] and the intravascular enhancement.[24]

The purpose of the present study was to systematically evaluate radiation dose reduction and image quality by using automated kVp-selection in CTA and, in addition, to evaluate if different CM injection protocols have an impact on radiation dose reduction and/or image quality. Therefore, fixed reference values of the kVp-selection algorithm, a normalised IDR and identical total iodine load (TIL; [gI]) were used. This study was performed in-vitro using a circulation phantom, ensuring high reproducibility and excluding patient-related variability, such as differences in the cardiovascular parameters or the patient size.

MATERIALS AND METHODS

Circulation phantom

A circulation phantom exhibiting physiological circulation parameters (heart rate 60 beats per minute [bpm] and blood pressure 120/80mmHg), as first described by Behrendt *et al*[25], was used. A modified version of this phantom was described in previous studies[26, 27] (**figure 3.1**).

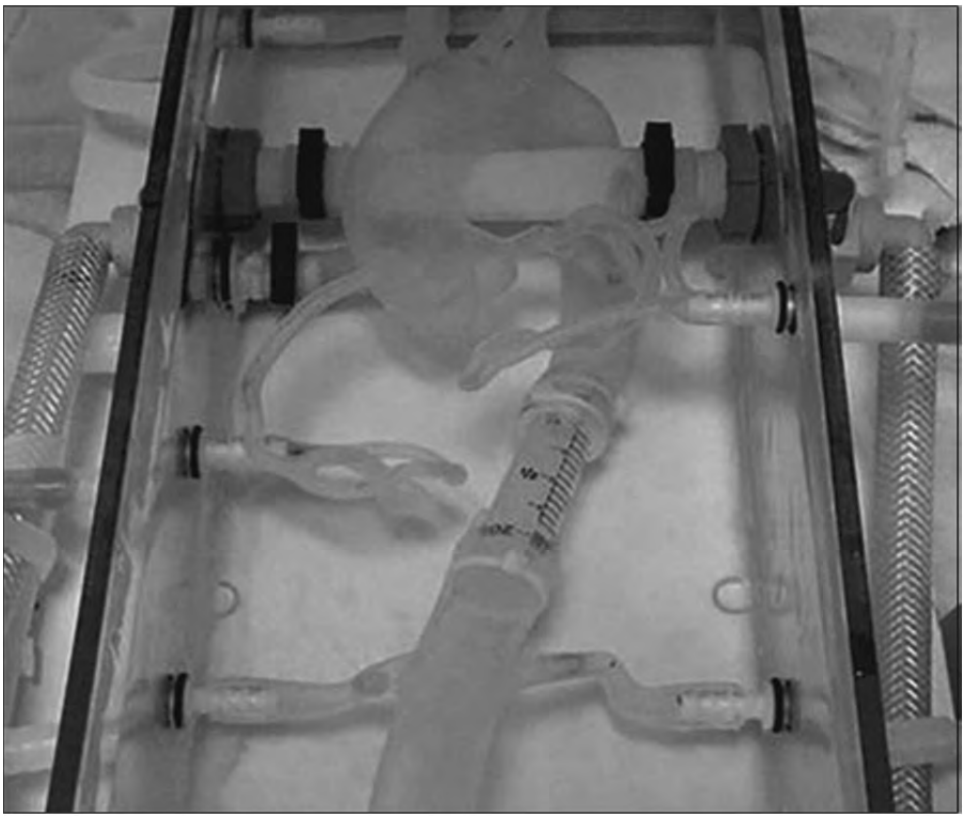

Figure 3.1 Acrylic container consisting of the circulation phantom, including replicas of the ascending and descending aorta, as well as the coronary and renal arteries

Injection and scan protocols

Non-ionic and low-osmolar CM were used (iopromide 300mgI/ml and 370mgI/ml [Ultravist; Bayer Healthcare, Berlin, Germany] and iomeprol 350mgI/ml and 400mgI/ml [Iomeron; Bracco Imaging, Milan, Italy]). The IDR and TIL in all groups were held constant (1.8gI/s and 20gI, respectively). The CM injection protocols are listed in **table 3.1**. CM was injected into the phantom using a standard CT power injector (MEDRAD Stellant, Bayer Healthcare, Indianola, PA, USA) via a three-way stopcock extension tube and a standard 18G needle (Sterican, Braun, Melsungen, Germany) into the injection port. The injection time was set to 11s for all injections throughout the experiment; a saline chaser at the same flow rate (injection time of 5s) was administered after every scan.

The CM was pre-heated to 37˚C. All relevant injection-related parameters (e.g. total amount of CM, flow rate, peak flow rate and peak pressure) were closely monitored using the Certegra™ Informatics Platform (Bayer Healthcare, Indianola, PA, USA). In addition, an independent data acquisition system (National Instruments Corporation, Austin, TX, USA) was used to monitor the physiological circulation parameters (e.g. blood pressure and heart rate) of the phantom throughout the experiments. After every scan, the vasculature of the phantom was flushed with water. Monitoring was needed for manual regulation of the preset (120/80mmHg) blood pressure during flushing.

CM concentration [mgI/ml]	CM Volume [ml]	Flow rate [ml/s]	IDR [gI/s]	Total iodine load [gI]	Injection time [s]
300 (Iopromide)	67	6.0	1.8	20.0	11.1
350 (Iomeprol)	57	5.1	1.8	20.0	11.1
370 (Iopromide)	54	4.9	1.8	20.0	11.1
400 (Iomeprol)	50	4.5	1.8	20.0	11.1

Table 3.1 Injection parameters for all CM protocols

A dynamic CT scan without table feed (120kVp, 210mAs), using a 2nd generation DSCT scanner (SOMATOM Definition Flash, Siemens Healthcare, Forchheim, Germany), was performed at the level of the heart. Based on the ROI signal measurement in the ascending aorta, the time to peak (TTP) for each CM concentration was determined. Then, helical CT scans of the thoraco-abdominal aorta were performed using a standard spiral examination protocol (128x0.6mm slice collimation, pitch 0.9, reference tube voltage 120kVp, qual. reference tube current 210mAs and gantry rotation time 500ms), which was separated into the following three protocols: (A) no dose modulation; (B) 3D tube current modulation (CAREDose4D™; and (C) automated tube voltage selection with 3D tube current modulation (CAREkV™). For the latter, the dose optimisation setting 11 (vessels) was used. The strength setting parameter in the CAREkV™ tool can vary between 1 and 12, where 12 is matching iodine CNR [19]. When selecting higher strength, the chance of lower tube voltage selection by the tool is higher and therefore as well the chance on reduced radiation dose. This study simulated dose reduction in CTA and therefore primary interest was iodine CNR, thus vessel setting (11) was selected. Furthermore, the dose reduction was predicted on the scan interface (see also figure 1 in[15]), a noise level prediction was not available.

Reconstruction was performed using an adapted field of view (FOV) of 2mm thick sections at increments of 1.4mm using a soft reconstruction kernel (Siemens B31f). All protocols were performed for each CM concentration (300, 350, 370 and 400mgI/ml) using the determined TTP in the ascending aorta (AA), including the initial scan delay (10s) as the delay time. All measurements were repeated three times.

Quantitative analysis

The dose-length product (DLP) was recorded for each protocol to calculate the effective dose [mSv]. The effective dose (E) was quantified by multiplying the DLP value and the conversion factor for the thorax (k = 0.014mSv/[mGy.cm]) and the abdomen (k = 0.015mSv/[mGy.cm]).[28] Because of the thoraco-abdominal scan range, an average conversion factor (k = 0.0145mSv/[mGy.cm]) was used. The attenuation [HU] was measured on all spiral CT-scan images by delineating a circular region of interest (ROI) in the lumen of the AA, coronary arteries (left main coronary artery [LM]), the descending aorta (DA), the abdominal aorta (AAo), the left renal artery (LRA) and the right renal artery (RRA). ROI were made as large as possible and placed centrally, in order to avoid the wall. Image noise was defined as a standard deviation (SD) of the attenuation. Signal-to-noise ratio (SNR) was calculated as vessel attenuation divided by image noise. In addition, the SNR per unit dose of radiation was calculated according to the following equation: SNR/(effective dose). Two experienced observers (MK, JT) who were blinded to each other's results independently analysed all ROI measurements. All dose-related parameters, such as the tube current, the tube voltage, the computed tomography dose index ($CTDI_{vol}$) and the DLP were reported directly from the scanner console after each scan.

Statistical analysis

All values are expressed as the means±SD. DLP, $CTDI_{vol}$ and effective dose for the various CM injection protocols and scan protocols was compared using the nonparametric Kruskal-Wallis one-way analysis of variance test by ranks. For post-hoc comparisons between scan protocols the Mann-Whitney U test was used. The mean attenuation values and the SNR in the AA, LM, DA, AAo, LRA and RRA, as well as for the different CM injection protocols, using the three scan protocols were compared via two-way ANOVA followed by the three-way Tukey test for post-hoc comparisons between the scan protocols, the CM injection protocols and the vascular segments. Intra-observer variability was assessed by calculating the intra-class correlation coefficients (ICC) using a two-way mixed model. The data analysis was performed using SPSS version 20.0 software (SPSS, Inc., Chicago, IL). All p-values are 2-sided, and a p-value of less than 0.05 was considered to be statistically significant.

RESULTS

All dose-related scan parameters are listed in **table 3.2**. Automated tube-current modulation (protocol B) caused the averaged tube-current time product to be reduced from 210mAs$_{ref}$ (protocol A) to 97±0.4mAs$_{eff}$ and, therefore, a significant reduction in the mean effective dose from 4.34±0.0mSv to 2.03±0.1mSv, with *p*-value <0.001. The use of automated kVp-selection (protocol C) caused the tube voltage to be reduced from 120kVp to 80kVp and 166±0.9mAs$_{eff}$, resulting in a significantly lower effective dose of 1.00±0.0mSv compared to protocols A and B with both *p*-values <0.001. Thus, the use of automated kVp-selection resulted in a 77% reduction in the radiation dose compared to the standard setting without dose modulation and a 51% reduction compared to tube current modulation alone.

Scan parameter	Protocol A*	Protocol B*	Protocol C*	P-value
kVp$_{ref}$ / mAs$_{ref}$	120 / 210	120 / 210	120 / 210	
kVp	120	120	80	
mAs$_{eff}$	210±0.0	97±0.4	166±0.9	
CTDI$_{vol}$ [mGy]	14.1±0.0	6.6±0.03	3.2±0.02	<0.001
DLP [mGy.cm]	299±0.04	140±0.6	69±0.4	<0.001
Effective Dose [mSv]	4.34±0.0	2.03±0.1	1.00±0.0	<0.001

Table 3.2 Dose related scan parameters for all three scan protocols in all CM concentrations
Values are expressed as mean±SD. The significant p-value involves differences between protocols A-B, A-C and B-C (results of post-hoc group comparison).
* Protocol A = no dose modulation; Protocol B = CAREDose4D^{TM} and Protocol C = CAREkV^{TM}

CM concentration [mgI/ml]	Effective Dose [mSv] Protocol A*	Effective Dose [mSv] Protocol B*	Effective dose [mSv] Protocol C*
300 (Iopromide)	4.34±0.0	2.03±0.1	1.00±0.0
350 (Iomeprol)	4.34±0.0	2.03±0.1	1.00±0.0
370 (Iopromide)	4.34±0.0	2.03±0.1	1.00±0.0
400 (Iomeprol)	4.34±0.0	2.04±0.1	1.00±0.0
p-value	0.30	0.40	0.27

Table 3.3 Effective dose for protocols A, B and C and for the different CM concentrations
Values are expressed as mean±SD. Protocol A = no dose modulation; * Protocol B = CAREDose4D™ and Protocol C = CAREkV™

The effective dose for each scan protocol and CM injection protocol are presented in **table 3.3**. The comparison between different CM injection protocols within the three scan protocols revealed no differences in the effective dose (**table 3.3**).
The mean attenuation values for protocols A (442.2±16.3HU) and B (428.2±14.5HU) were nearly identical, whereas significantly higher attenuation values were observed for protocol C (747.0±25.6HU), with $p<0.001$ for all vascular segments (between protocol A-C and B-C) (**figure 3.2**).
No significant differences were detected in the attenuation values between the different CM injection protocols (300, 350, 370 and 400mgI/ml) for any of the three scan protocols or any of the vascular segments; all p-values ≥0.78 (**figure 3.2**).
The mean SNR was higher for protocol A (54.7±10.9) than for protocols B (43.4±7.1) and C (42.9±5.1). This difference was significant in four of the six vascular segments: AA, DA, AAo and RRA. The corresponding eight p-values for all four segments and between protocols A-B and A-C were all <0.001. No statistically significant differences in the SNR were found between the different CM injection protocols for any of the three scan protocols or any of the vascular segments; all p-values ≥0.59 (**figure 3.3**).

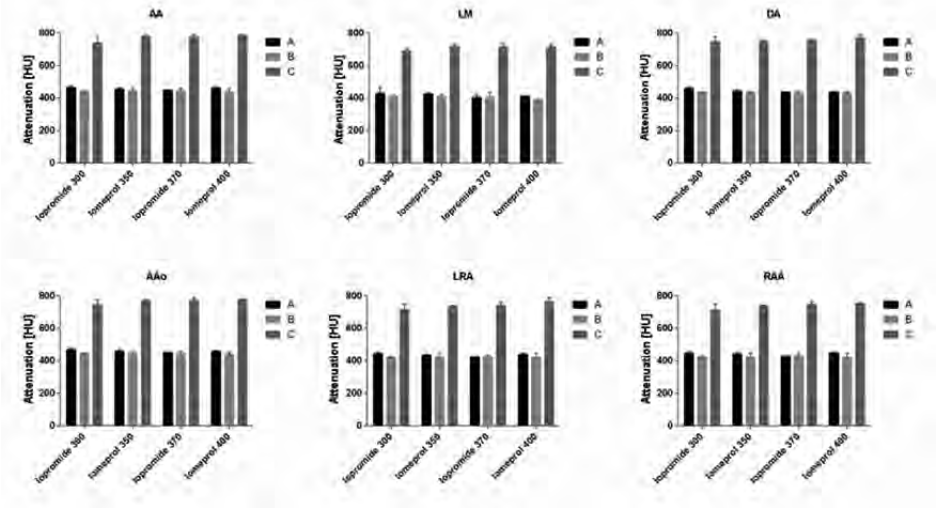

Figure 3.2 Bar graphs displaying the difference in the attenuation values between the scan protocols (A, B, and C) and the CM injection protocols for each vascular segment
There were significantly higher attenuation values for protocol C compared to the other two protocols ($p<0.001$) in each vascular segment. No significant differences were found in the attenuation values between the different CM

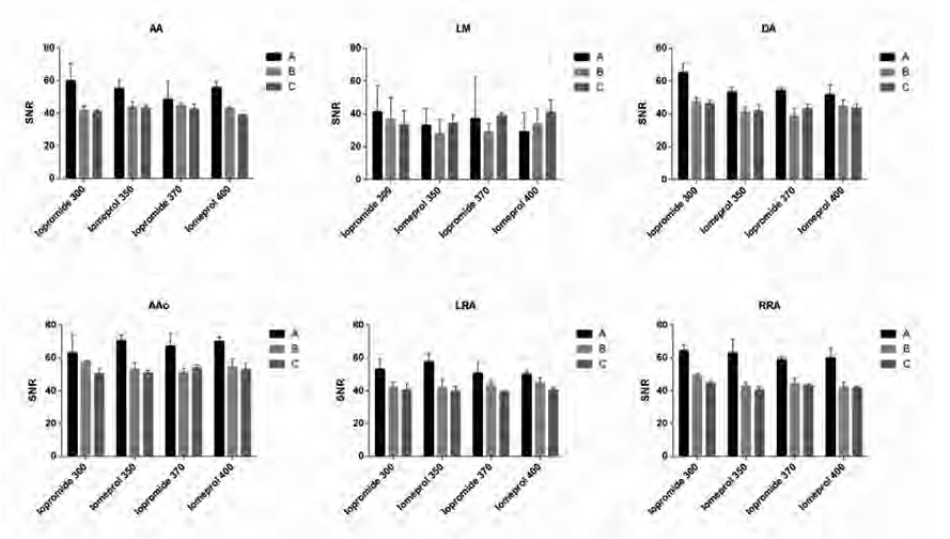

Figure 3.3 Bar graphs displaying the difference in the SNR between the scan protocols (A, B and C) and the CM injection protocols for each vascular segment
There were significantly higher SNR values for protocol A compared to the other two protocols in the AA, DA, AAo and RRA ($p<0.001$). No significant differences were found in the SNR between the different CM

The mean SNR per unit radiation dose, a measure of the dose effectiveness, was higher in protocol C (41.6±4.9mSv^{-1}) than in protocols B (20.6±3.4mSv^{-1}) and A (12.2±2.4mSv^{-1}). The corresponding eighteen *p*-values for all six segments between protocols C-B; C-A and A-B were all <0.001. This difference was independent of the CM injection protocol, all p >0.421 (**figure 3.4**). The reproducibility of the attenuation measurements was very high, with an intra-observer correlation of 0.997.

The TTP did not differ between the dynamic scans and was determined to be 14s for each CM concentration and protocol. The analysis of the injection parameters revealed only minor, negligible differences between the planned and applied CM volumes and flow rates (**table 3.4**). However, the injection pressure differed significantly between the CM injection protocols, except from the difference between 300 and 370mgI/ml (**table 3.4**). The highest peak pressure (104±2.5psi) was recorded for the protocol using highest concentration of CM, whereas the lowest pressure (82±2.1psi) was detected for the 350mgI/ml concentration protocol. The monitoring of heart-rate and blood pressure reveals no deviation from the defined values.

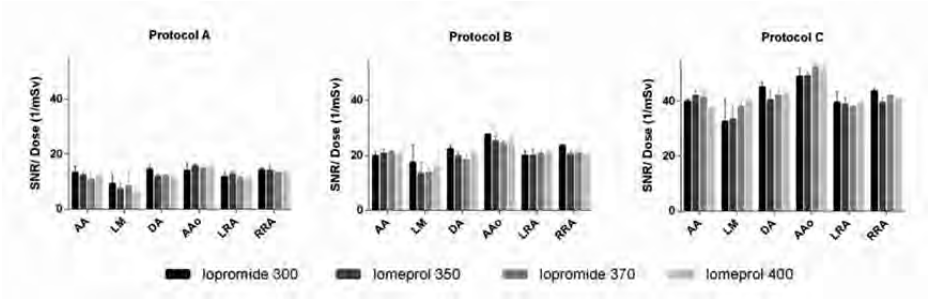

Figure 3.4 Bar graphs displaying the difference in the SNR normalised to the effective radiation dose (Dose) between the four different CM injection protocols in all vascular segments for each scan protocol
The SNR/Dose ratio was significantly higher (p<0.001) for protocol C compared to the other two protocols. No significant differences in the SNR/dose ratio were found between the different CM

CM Concentration [mgI/ml]	Time to peak, TTP [s]	Applied volume [ml]	Applied flow rate [ml/s]	Peak pressure [psi]
300 (Iopromide)	14	67.0±0.1	5.6±0.1	95±1.5
350 (Iomeprol)	14	56.9±0.1	4.8±0.1	82±2.1
370 (Iopromide)	14	54.0±0.1	4.7±0.1	92±2.7
400 (Iomeprol)	14	49.9±0.1	4.3±0.0	104±2.5

Table 3.4 Time-to-peak analysis and injection parameters recorded using the Certegra^{TM} Informatics Platform
Values are expressed as mean±SD

DISCUSSION

In this phantom study, the potential for automated kVp-selection to reduce the radiation dose during CTA using different concentrated CM normalised to an identical IDR was evaluated. Therefore, automated kVp-selection (CAREkV^{TM}) was compared to the well-established automated tube current modulation alone (CAREDose4D^{TM}) and referenced to the standard CT settings without dose modulation.
In contrast to clinical studies, our measurement setup allows for the repeated injection of CM under highly standardised conditions, thus enabling an evaluation of different CM injection protocols to explore radiation dose reduction and signal enhancement. The phantom resembles the human condition with respect to the vascular architecture, the circulation parameters (heart rate, stroke volume and blood pressure) and the applied injection parameters (IDR, total amount of iodine and power injection via an 18G i.v. line).[27] Additionally, the reference settings of the CT-scan (kVp_{ref}, mAs_{ref}) are equivalent to the settings for human thoracic abdominal CTA. Thus, the measurement setup and procedures are comparable to the clinical condition.
Although both dose modulation techniques significantly reduced the radiation dose, automated kVp-selection was much more effective than automated tube current modulation alone, both being independent of the CM injection protocol. Using protocol C, the tube voltage was automatically reduced from 120 to 80kVp. Consequently, the vascular attenuation for protocol C is higher than for protocols A and B. On the other hand, the highest SNR was observed for protocol A However, a SNR greater than 30, which was found in each scan protocol (A, B, and C) ensures appropriate image quality.[29]

As we could show, automated kVp-selection has a higher dose reducing potential compared to tube current modulation**,** as both kVp and tube current could be reduced at the same time.[15] However, switching to lower kVp settings using automated kVp-selection is only feasible over the whole scan length, while tube current modulation gives the opportunity to reduce tube current [mAs] per slice.[30, 31] For example, in patients with increased BMI, weight or abdominal diameter, the possibility arises that the scanner won't be able to reduce tube voltage, as x-ray tube power is limited and image noise may increase.[9] Then, both algorithms may result in identical radiation doses as automated kVp-selection includes also automatic tube current modulation. If maximum kVp switching is desired with regards to optimise radiation dose, only the relatively thin patients will benefit from the current results. In patients with a normal to higher BMI, the maximum radiation dose reduction will be limited as the scanner will not switch to 80kVp. However, the recently introduced high power x-ray tubes have the potential to overcome this limitation and the number of patients who will benefit from such a maximum radiation dose reduction can only be expected to increase in the future.[22]

Automated kVp-selection requires an important user input; settings as kVp and mAs reference values must be defined. These parameters determine the noise level and directly impact the calculation of the required scan parameters for automated tube current modulation and automated kVp-selection. In our study, the standard settings for abdominal scans (120kVp and 210mAs) used in protocol A were used as reference values for protocols B and C to ensure a meaningful comparison of the two dose modulation algorithms. The impact of the reference settings on the automated tube voltage selection was investigated in a study by Schwarz *et al.*[32] They found that a reduction in the reference tube-current time product from 330 to 250mAs results in an increased use of lower tube voltages and therefore a reduction in the radiation dose. However, this reduction was accompanied by a significant increase in the image noise. In contrast to our study, Schwarz *et al*[32] increased the IDR and the TIL by administering 400mgI/ml CM applied at the same flow rate and volume as 300mgI/ml CM. This significant increase in the TIL compensated for the higher noise and maintained the SNR.

For the evaluation of automated dose modulation algorithms for CTA, the radiation dose and the SNR must be considered. Therefore, the SNR-to-dose ratio was introduced, which takes both parameters into account. Considering protocol A as a reference, the SNR-to-dose ratio was increased by a factor of 2 for protocol B and a factor of 3.4 for protocol C independent of the CM concentration that were administered at normalised IDR.

For CTA, in which the attenuation primarily depends on the intravascular iodine concentration, the greatest reduction in the radiation dose can be achieved. Consequently, the contrast injection protocol plays a major role. In clinical practice, different CM concentrations, ranging between 300 and 400mgI/ml, are routinely used during CTA.

The key parameters that determine the vascular signal enhancement are the IDR and the TIL.[33, 34] Therefore, the injection rate and volume in our study were adapted to the CM concentration, whereas the IDR, the TIL and the injection time were held constant. The resulting intravascular attenuation did not differ between the CM concentrations for either the reference measurement (protocol A) or the dose modulation protocols (protocol B / C). Consequently, we conclude that the vascular attenuation, the automated tube voltage selection-mediated dose reduction and the image quality are independent of the CM concentration when a normalised IDR is used. This finding is quantitatively described by the nearly identical SNR-to-dose ratios for the different CM concentrations.
The different physicochemical properties of different concentrated CM, in particular the increasing viscosity for higher iodine concentrations may have an impact of the bolus profile[23] and enhancement.[24] In our phantom study, no differences in time-to-peak or vascular attenuation between the different concentrations of CM were detected. However, the injection pressure differed between the CM concentrations; the highest peak pressure was found for 400mgI/ml, which could be explained by its highest viscosity.[27]

Limitations

In this experiment, all scans were performed on a circulation phantom. This phantom, which contains controllable and consistent physiological parameters, does not provide the physiological and anatomical heterogeneity of a standard population. Therefore, the effects of different BMIs on dose reduction were not evaluated.

CONCLUSION

These results show that automated tube current modulation can result in radiation dose reduction up to 53% and automated tube voltage selection up to 77%, if human subjects approximate the dimensions and therefore the attenuation values of the phantom used in this experiment. Dose reduction was – as expected – independent of the CM concentration applied at normalised IDR.

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CHAPTER 4

Optimising contrast media application in coronary CT angiography at lower tube voltage: evaluation in a circulation phantom and sixty patients

Kok M, Mihl C, Hendriks BMF, Altintas S, Kietselaer BLJH, Wildberger JE, Das M. *Eur J Radiol*. 2016 Jun;85(6):1068-74.

ABSTRACT

Purpose

The purpose was to investigate optimal contrast media (CM) injection parameters for lower kVp settings, whilst maintaining diagnostic attenuation levels.

Methods and materials

First, a circulation phantom with physiological parameters (BP 120/80mmHg, HR 60bpm) was used. A fixed CM injection protocol was used for each kVp setting (300mgI/ml [Iopromide], volume=45ml, flow rate=6.0ml/s, iodine delivery rate (IDR)=1.8gI/s, iodine load=13.5gI; at 120, 100, 80 and 70kVp). Then, IDR was decreased by steps of 0.2gI/s for each kVp setting, until diagnostically insufficient attenuation values were reached (<325HU). In order to keep injection time constant (7.5s), total iodine load (TIL) was reduced accordingly.
Second, clinical applicability at 120 and 100kVp was evaluated in patients (n=60) referred for coronary CT angiography. A standard and reduced (12% less) CM protocol was used based on weight classes and scan duration ('high-pitch': 1s; 'adaptive sequence' and 'helical': 7s). Attenuation levels of the coronary arteries were measured and compared between protocols.

Results

Using a fixed CM injection at each kVp level resulted in the following values (HU±SD): 335±31 (120kVp); 425±30 (100kVp); 587±29 (80kVp); 666±27 (70kVp). Keeping diagnostic enhancement levels (353±28) CM could be reduced as follows: 12% for 100kVp; 45% for 80kVp and 56% for 70kVp. Diagnostic enhancement levels could be reproduced with concurrent CM reduction (-12% at 100kVp) in the clinical setting (382±35).

Conclusion

CM injection parameters can be substantially reduced at low kVp settings (up to 56% at 70kVp), whilst maintaining diagnostic attenuation levels. This may play an important role in CT imaging of the coronary arteries as well as cerebral and peripheral circulations in the future.

INTRODUCTION

Lowering tube voltage [kVp] in CT angiography (CTA) increases the degree of vascular contrast enhancement.[1-3] This is explained by the fact that lower kVp translates into lower effective photon energy (effective photon energy being approximately half the kVp), bringing the latter closer to the K-edge of Iodine (33.2keV).[4,5] Thus, at lower kVp settings comparable attenuation values can theoretically be reached using less contrast media. Reducing the amount of CM whilst maintaining optimal diagnostic enhancement values is desirable as it may increase patient safety, reducing the risk of contrast-induced nephropathy (CIN)[6], and reduce variable costs.

Theoretically, there are different ways in which CM injection protocols may be adapted for CTA. Important parameters are CM volume [ml], total iodine load (TIL = total iodine in gI), and iodine delivery rate (IDR= the amount of iodine injected per second [gI/s] = concentration of CM*flow rate in ml/s). In this respect, multiple studies indicated that the IDR can be considered as the most decisive parameter in attenuation of the vascular structures.[7-11] IDR can be adapted solely or in a combined fashion with TIL. If adapted separately, however, overall injection time is influenced as well. This is undesirable, injection time being a decisive injection protocol parameter, optimised for the target organ in combination with the scan protocol chosen. Adapting TIL and IDR simultaneously, however, will allow injection time to remain constant. Furthermore, using a combination of TIL and IDR in study design ensures uniformity even when different CM types are used.

The use of lower kVp settings in CTA has become more popular, however, image noise increases at lower kVp settings, mainly due to higher absorption of low-energy photons by the patient.[12] Nowadays, new reconstruction technologies such as iterative reconstruction (IR) improve image quality in comparison to routinely used filtered back projection (FBP), as IR reduces image noise.[13-16] This may help in maintaining diagnostic image quality whilst using reduced radiation dose.

The purpose of this study was to systematically investigate how to optimise CM injection parameters at lower kVp settings. First, a circulation phantom was used, ensuring high reproducibility, standardisation, and, therefore, excluding patient-related variability. Second, based on the results of the in vitro study, the clinical applicability was evaluated in a patient population at 120kVp and 100kVp in combination with IR.

METHODS AND MATERIALS

Study design

The systematic approach of optimising CM injection parameters to lower kVp settings was assessed in vitro with a circulation phantom. Reproducibility of optimised CM injections was evaluated in vivo.

In vitro setup

Circulation phantom

A circulation phantom with physiological circulation parameters was used (heart rate 60 beats per minute [bpm], blood pressure 120/80mmHg) as first described by Behrendt *et al*[17] In recent years this phantom has been modified and validated in several experiments.[8,9] The vasculature of the phantom consists of replicas of the ascending and descending aorta, the coronary arteries including left main coronary artery (LM); left anterior descending artery (LAD); circumflex artery (Cx) and right coronary artery (RCA), renal arteries and common iliac arteries.

Scan and CM injection protocol

Spiral CT scans of the coronary arteries were performed using a 2nd generation dual source CT (DSCT) scanner (SOMATOM Definition Flash, Siemens Healthcare, Forchheim, Germany). A 3D reconstruction of the phantom aortic root and coronary elements is shown in **figure 4.1.**

A tissue equivalent ring was placed around the area of the coronary elements to simulate body surface. A clinically used examination protocol was applied with the following scan parameters: 128x0.6mm slice collimation; gantry rotation time 0.28s and pitch value 0.23. An automated tube current modulation (CareDose4D, Siemens) was switched off in the phantom experiments and the chosen effective tube-current-time product varied for the different kVp settings between 284-370mAs$_{eff}$: 320mAs$_{eff}$ for 120 and 100kVp settings, reference tube-current-time product [mAs$_{ref}$] being 320 in clinical routine. For 80 and 70kVp settings, 370 and 284mAs$_{eff}$ were chosen respectively, these values being the highest technically feasible tube-current-time product at these low kVp settings using this dedicated scanner. Image reconstruction was carried out using 0.75mm slice thickness and an increment of 0.5mm using an raw-data based iterative reconstruction mode (kernel: I26f SAFIRE iterative reconstruction strength 2).

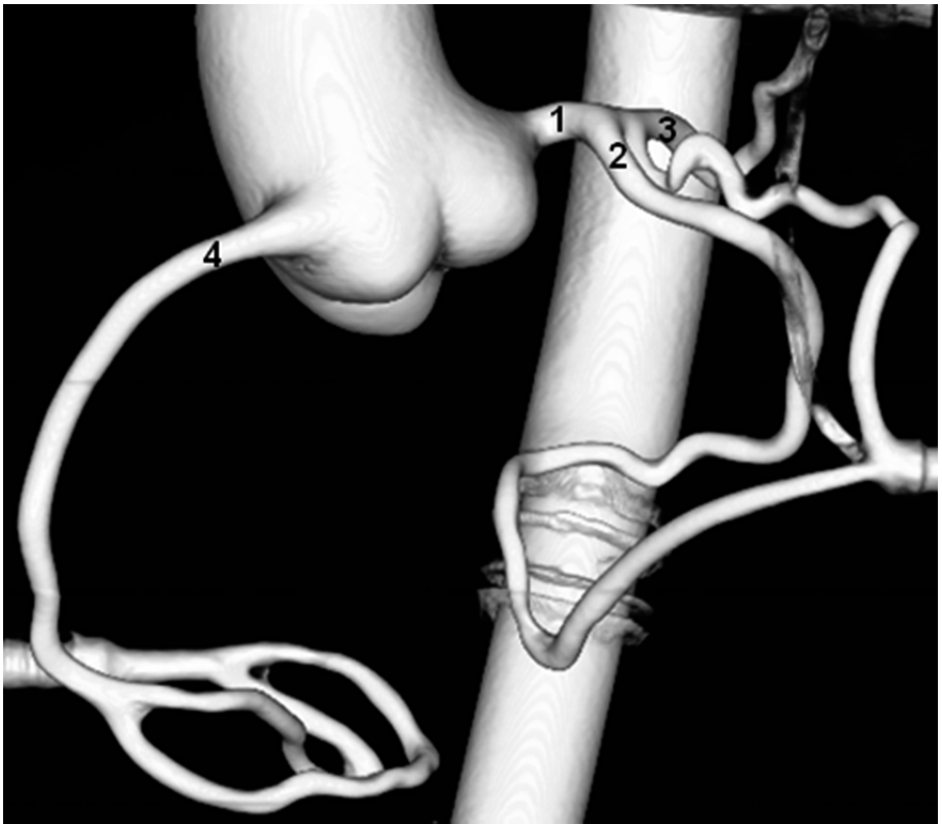

Figure 4.1 A 3D reconstruction of the circulation phantom used
1 = LM; 2 = LAD; 3 = Cx and 4 = RCA

CM with an iodine concentration of 300mgI/ml (Iopromide, Ultravist, Bayer Healthcare, Berlin, Germany) was applied at different kVp settings (120, 100, 80 and 70kVp). After being warmed to body temperature (37°C/99˚F), CM was injected into the circulation phantom using a standard CT power injector (Stellant, MEDRAD, Pittsburgh, PA, USA), a three-way stopcock extension tube and a standard 18G needle (Sterican, Braun, Melsungen, Germany), under the following standardised conditions: First, one and the same CM injection protocol was used at each kVp setting (CM volume: 45ml, flow rate: 6.0ml/s, IDR: 1.8gI/s and TIL: 13.5gI, at 120, 100, 80 and 70kVp). Second, based on the differences in attenuation values for these first scans, a specific starting point for IDR and TIL was chosen for the lower kVp settings (100, 80 and 70kVp): 1.8gI/s and 13.5gI for 100kVp; 1.2gI/s and 9gI for 80kVp; and 1.0gI/s and 7.5gI for 70kVp. IDR was then decreased by steps of 0.2gI/s for each kVp setting, until diagnostically insufficient attenuation values were reached (<325HU)[18-20]; TIL was reduced accordingly in order to keep injection time constant (7.5s). Before each injection pro-

tocol, test bolus technique was used to determine the particular scan delay for each flow rate using 10ml of CM. After each scan, a saline chaser was injected at the same flow rate, injection time 3s. All flow rates and CM injection protocols used are listed in **table 4.1** and were closely monitored during the experiments by using the Certegra™ Informatics Platform (Bayer). All protocols were repeated five times in order to determine reproducibility.

Tube Voltage [kVp]	Injection Parameter Reduction [%]	CM Volume [ml]	Flow rate [ml/s]	IDR [gI/s]	TIL [gI]	Delay [s]	Injection Time [s]
120	**0**	**45**	**6.0**	**1.8**	**13.5**	**16**	**7.5**
100	0	45	6.0	1.8	13.5	16	7.5
	12	**40**	**5.3**	**1.6**	**12**	**17**	**7.5**
	23	35	4.7	1.4	10.5	17	7.5
80	34	30	4.0	1.2	9	18	7.5
	45	**25**	**3.3**	**1.0**	**7.5**	**19**	**7.5**
	56	20	2.7	0.8	6	20	7.5
70	45	25	3.3	1.0	7.5	19	7.5
	56	**20**	**2.7**	**0.8**	**6**	**20**	**7.5**
	67	15	2.0	0.6	4.5	24	7.5

Table 4.1 Injection parameters used at the different kVp settings in the phantom experiments

Data processing

Dose related parameters such as computed tomography dose index ($CTDI_{vol}$) and dose length product (DLP) for 120, 100, 80 and 70kVp settings were recorded directly from the scanner console after each scan; injection related parameters were read out after each scan. Attenuation values (HU±SD) of CT-scan images were measured by delineating circular regions of interest (ROI) placed in the centers of the LM, LAD, Cx and RCA, using the source images on a dedicated post processing workstation (SyngoVia™, Siemens). SNR was calculated by dividing attenuation values by their standard deviations. In addition, background attenuation values (HU_{water}) and image noise (SD_{water}) were measured by delineating a circular region of interest (ROI) in the water-filled container. CNR was defined as the attenuation value of the enhanced vessel (HU_{vessel}), minus the background attenuation value, divided by background image noise (SD_{water}).

Phantom images were independently analysed by two blinded experienced observers (MK, BH).

Statistical analysis

All continuous variables are reported as mean ± standard deviation (SD). Intra-observer variability was evaluated by calculating intraclass correlation coefficients (ICC), using a two-way mixed model (SPSS version 20.0, SPSS Inc, Chicago, IL, USA).

Validation of the reproducibility of optimised CM injections: an in vivo setup

Patients

Clinical applicability was evaluated in a patient population (n=60). Patients referred for coronary CTA (CCTA) with stable symptoms of chest discomfort and suspected coronary artery disease (CAD), were included. Baseline characteristics such as age, weight and heart rate were recorded for each patient.

Ethical approval was given and informed consent for the use of (coded) images was waived by the local ethical committee, as the data was analysed anonymously in accordance with the Institutional Review Board guidelines (METC 14-4-049).

Scan and CM injection protocol

For the assessment of the coronary arteries, scans were performed using the same scanner as was used in the phantom experiments. Scan parameters were as follows: 128x0.6mm slice collimation; 320mAs_{ref}; gantry rotation time 0.28s; pitch value 0.23 (''helical'') or 3.4 (''high-pitch''); and a variable scan delay according to the test bolus method. An automated tube current modulation (CareDose4D, Siemens) was switched on. Image reconstruction was carried out with individually adapted FOV at 0.75mm slice thickness and an increment of 0.5mm using an raw-data based iterative reconstruction mode (kernel: I26f SAFIRE iterative reconstruction strength 2).

In patients with a stable heart rate of <60 beats per minute [bpm], a prospectively ECG-triggered “high pitch” spiral protocol was used. In patients with a stable heart rate of 60-90bpm, a prospectively triggered “adaptive sequence” protocol was used (prospective sequential data acquisition). In patients with an irregular heart rate, or with a stable heart rate of >90 bpm, a retrospectively gated “helical” protocol was used. All patients received an oral dose of 50 mg metoprolol tartrate (Selokeen; AstraZeneca, Zoetermeer, The Netherlands), two hours before CCTA. When indicated, an additional dose of 5-20mg metoprolol tartrate was administered intavenously with the aim to lower the heart rate to <60bpm, if possible. A maximum dose of 0.8mg nitroglycerine (Isordil®, Pohl-Boskamp**,** Hohenlockstedt, Germany) was given sublingually just prior to CCTA. Heart rate and ECG were monitored during CCTA.

Prewarmed CM (300mgI/ml at 37˚C [99˚F]) was injected with a standard CT power injector, a three-way stopcock extension tube, and a standard 18G needle. Patients were divided into three groups (n=20 for each group). Group 1 (120kVp) and group 2 (100kVp) received our standard clinical injection protocol for CCTA, which is based on the weight of the patient and duration of the CT data acquisition (P3T Cardiac™, Bayer). Group 3 (100kVp) received a reduction protocol, in which the standard injection protocol parameters CM volume, IDR and TIL were reduced by the percentage found in the experimental setup for 100kVp. The clinical applicability of the 80kVp and 70kVp protocols was not tested due to technical limitations of the current used scanner in the experiments: it is not feasible for the current scanner to apply the necessary tube-current-time products for all patients in order to maintain diagnostic image quality in lower kVp settings.
The details of each protocol are given in **table 4.2**. Scan delay was determined by using test bolus technique (20ml of CM in combination with the calculated flow rate). All injection parameters were closely monitored using a dedicated informatics platform (Certegra™, Bayer).

Data processing
Injection related parameters were read out after each scan. Images were analysed by using the source images on a dedicated post processing workstation (SyngoVia™, Siemens).
Subjective image quality of the images was determined by rating the presence of artefacts using a 4-point grading-scale: 1 = non diagnostic image quality; 2 = reduced image quality due to major artefacts, but still diagnostic; 3 = good image quality with minor artefacts and 4 = excellent image quality without artefacts. Image quality was rated in consensus by an experienced radiologist and cardiologist. Objective image quality was determined by measuring intravascular enhancement of the coronary arteries using manually placed ROIs at the levels of the LM, LAD, Cx and RCA. Measurements were performed by placing ROIs in the center of each vessel – using the maximum possible diameter and while avoiding the vessel wall (see also **figure 4.2**). Background attenuation levels and image noise – required for the calculation of CNR – were measured by delineating a circular region of interest (ROI) in pectoral muscle. Diagnostic image quality was considered sufficient at attenuation values >325HU[18-20] and CNR >10.[21]
Objective image quality was independently analysed by two blinded experienced observers (MK, BH).

Injection protocol	CM bolus [ml]	Mixed bolus (20%CM) [ml]	Total volume (CM) [ml]	Saline flush [ml]	Flow rate [ml/s]	IDR [gI/s]	TIL [gI]
Standard (Groups 1 and 2)							
60-74 kg							
'adaptive/helix'	56	67 (13.4)	123 (69.4)	40	5.6	1.7	22
'flash'	45	67 (13.4)	112 (58.4)	40	5.6	1.7	20
75-94 kg							
'adaptive/helix'	66	84 (16.8)	150 (82.8)	40	6.6	2.0	23
'flash'	53	84 (16.8)	137 (69.8)	40	6.6	2.0	21
12% reduction (Group 3)							
60-74 kg							
'adaptive/helix'	49	59 (11.8)	108 (60.8)	40	4.9	1.5	22
'flash'	40	59 (11.8)	99 (51.8)	40	4.9	1.5	20
75-94 kg							
'adaptive/helix'	58	74 (14.8)	132 (72.8)	40	5.8	1.7	23
'flash'	46	74 (14.8)	120 (60.8)	40	5.8	1.7	21

Table 4.2 Injection protocol parameters according to patient body weight

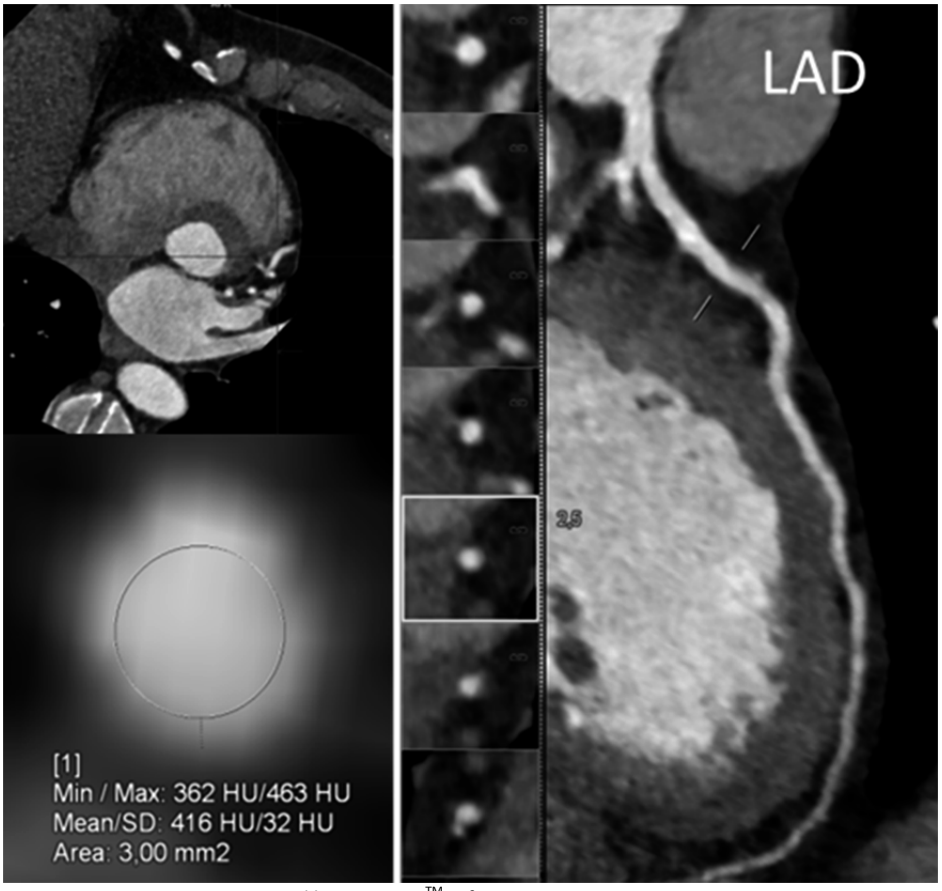

Figure 4.2 Images as reconstructed by Syngo-Via™ software
An axial multiplanar reconstruction (MPR) at the level of the LAD *(left, top image)*; a straightened-MPR of the LAD with a given landmark *(right image)* and an orientated cross-section of the landmark including the ROI measurement *(left, bottom image)*

Statistical analysis

All continuous variables are reported as mean ± standard deviation (SD). Objective image quality measurements and baseline characteristics (e.g. weight, age and heart rate) were compared between groups using one-way ANOVA followed by Tukey test for post hoc comparisons between groups. Differences in the division of scan protocols and subjective image quality were compared between groups using a Chi-Square test. Intra-observer variability was evaluated by calculating intraclass correlation coefficients (ICC), using a two-way mixed model (SPSS version 20.0, SPSS Inc, Chicago, IL, USA).

RESULTS

In vitro setup

Radiation dose decreased with 83% when lowering kVp settings from 120kVp to 70kVp. Corresponding CTDIvol and DLP (mean±SD) were as follows: 71±1 and 1088±18 (120kVp); 43±2 and 658±24 (100kVp); 24±2 and 363±37 (80kVp); 12±1 and 181±18 (70kVp).

Using identical injection parameters, attenuation values (HU±SD) were as follows: 335±31 (120kVp); 425±30 (100kVp); 587±29 (80kVp); 666±27 (70kVp) (see **figure 4.3**). After stepwise reduction of IDR for lower kV settings, the minimum IDR and TIL values yielding diagnostically sufficient attenuation values were estimated to be as follows (see **table 4.1**, bold): 1.6gI/s and 12gI for 100kVp; 1.0gI/s and 7.5gI for 80kVp; 0.8gI/s and 6.0gI for 70kVp. Corresponding attenuation values were in the range of 360±27 and 382±35HU for all vascular segments. (see **table 4.3**, bold). After post hoc comparisons, significant lower attenuation values were found in the LAD and Cx of 120kVp compared the other kVp settings, with *p*-values ≤0.01. TIL and IDR could be decreased at lower kV settings as compared to at 120kVp, yielding diagnostically sufficient attenuation values: 12% at 100kVp, 45% at 80kVp, and 56% at 70kVp.

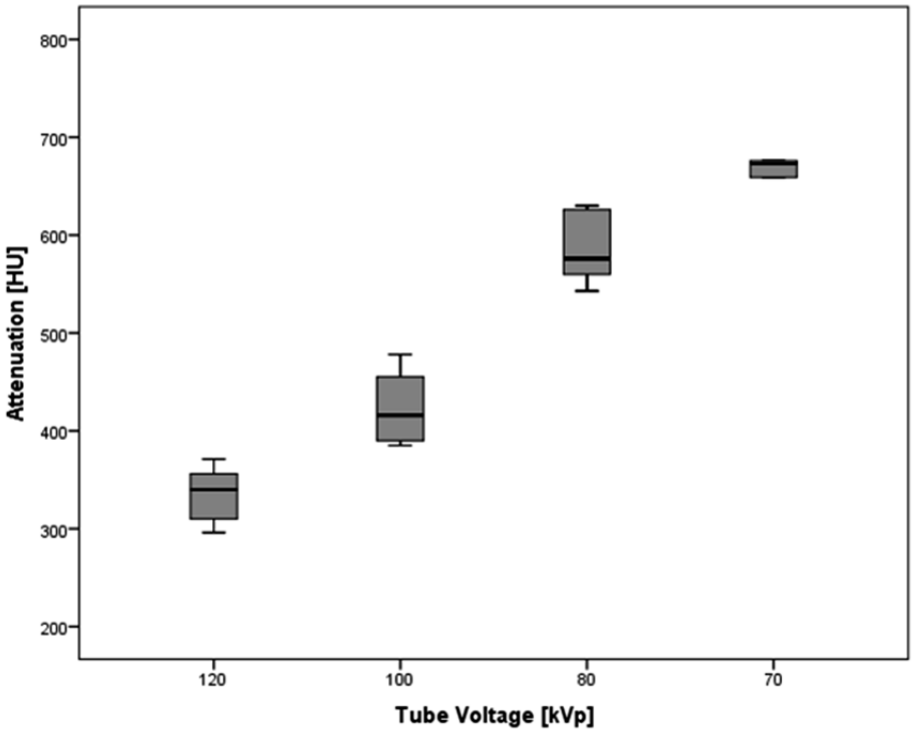

Figure 4.3 Mean attenuation values at different kVp settings
Identical injection parameters were used (CM volume: 45ml, flow rate: 6.0ml/s, IDR: 1.8gI/s and TIL: 13.5gI) in phantom

SNR and CNR decreased with lowering kVp: 17±3 and 21±2 (120kVp); 13±3 and 16±4 (100kVp); 10±2 and 11±2 (80kVp) and 5±1 and 8±1 (70kVp), with *p*-values <.001 (see **table 4.3**, bold). Reproducibility of image quality measurements proved to be very good: intraclass correlation was high (0.993).

Tube Voltage [kVp]	Injection parameter reduction [%]	LM [HU]	LAD [HU]	Cx [HU]	RCA [HU]	SNR	CNR
120	**0**	**335±31**	**337±29**	**327±20**	**354±27**	**17±3**	**21±2**
100	0	425±30	422±23	419±29	463±23	16±3	18±4
	12	**377±22**	**360±30**	**362±16**	**365±27**	**13±3**	**16±4**
	23	319±27	315±17	323±34	320±18	13±4	14±1
80	34	434±26	436±28	408±36	430±23	10±1	13±2
	45	**375±28**	**360±30**	**381±25**	**382±35**	**10±2**	**11±2**
	56	290±29	272±33	294±30	288±11	6±1	9±1
70	45	446±29	443±29	438±30	470±17	6±1	10±1
	56	**379±14**	**375±30**	**376±19**	**377±29**	**5±1**	**8±1**
	67	284±31	274±30	280±24	284±31	4±1	5±2
p-value		.003^	0.19	.003^	0.48	<.001	<.001

Table 4.3 Attenuation values of vascular segments at 70, 80, 100 and 120kVp
Values are expressed as mean±SD. According the injection parameters of **table 4.1**.
* P-values were based on the differences between attenuation values of different kVp settings – provided in the middle row of each kVp setting (bold)
^ Significant differences were only found between 120kVp and 100, 80 and 70kVp

In vivo setup

Mean body weight of groups 1, 2 and 3 was: 84±6kg (range: 75–90); 83±5kg (range: 75–90) and 79±4kg (range: 73 – 87) respectively. All baseline characteristics are listed in **table 4.4**. Significant lower weight was found for group 3 compared to the other two groups (p=0.04).

Mean CTDIvol and DLP (mean±SD) for 120kVp (group 1) and 100kVp (group 2 and 3) were as follows: group 1: 11±1 and 121±16 ('high-pitch'), 52±6 and 467±103 ('adaptive'); group 2 and 3: 6±1 and 59±7 ('high-pitch') and 33±11 and 270±97 ('adaptive'/'helical').

Baseline characteristics				
	Group 1 (n = 20)	Group 2 (n = 20)	Group 3 (n = 20)	p-value
Age [y]	57±10	55±11	55±9	0.81
Weight [kg]	84±6	83±5	79±4	0.04
Heart rate [bpm]	60±6	58±6	61±8	0.29
Scan protocol applied				
	Flash 16 (80%) Adaptive 4 (20%)	Flash 16 (80%) Adaptive 4 (20%)	Flash 14 (70%) Adaptive 4 (20%) Helix 2 (10%)	0.38

Table 4.4 Baseline characteristics of study patient groups and applied scan protocols
Values are expressed as mean±SD or n; (percentage)

Subjective image quality is shown in **figure 4.4** and all datasets were diagnostic, no significant difference was found in image quality between groups (*p*=0.94). **Figure 4.5** shows mean attenuation values for all three groups. Using identical injection parameters, attenuation values (HU±SD) were: Group 1: 328±21 (LM), 320±29 (LAD), 322±24 (Cx), and 330±31 (RCA); Group 2: 421±29 (LM), 426±37 (LAD), 420±45 (Cx), and 434±14 (RCA). Applying a 12% reduction in TIL and IDR at 100kVp, provided attenuation values as follows: 369±38 (LM); 353±28 (LAD); 354±29 (Cx); and 355±39 (RCA). Significant differences in attenuation values were found between al groups, with *p*-values <.001. **Figure 4.6** shows mean SNR and CNR for all three groups. Mean SNR and CNR were as follows: 17±7 and 23±6 (group 1); 18±7 and 19±7 (group 2) and 18±11 and 15±4 (group 3). Significant differences were found in CNR between all groups, with *p*-values <.001. No significant differences were found in SNR between the three groups, with *p*-values ≥0.58.

Reproducibility of objective image quality measurements proved to be very good: intraclass correlation was high (0.986).

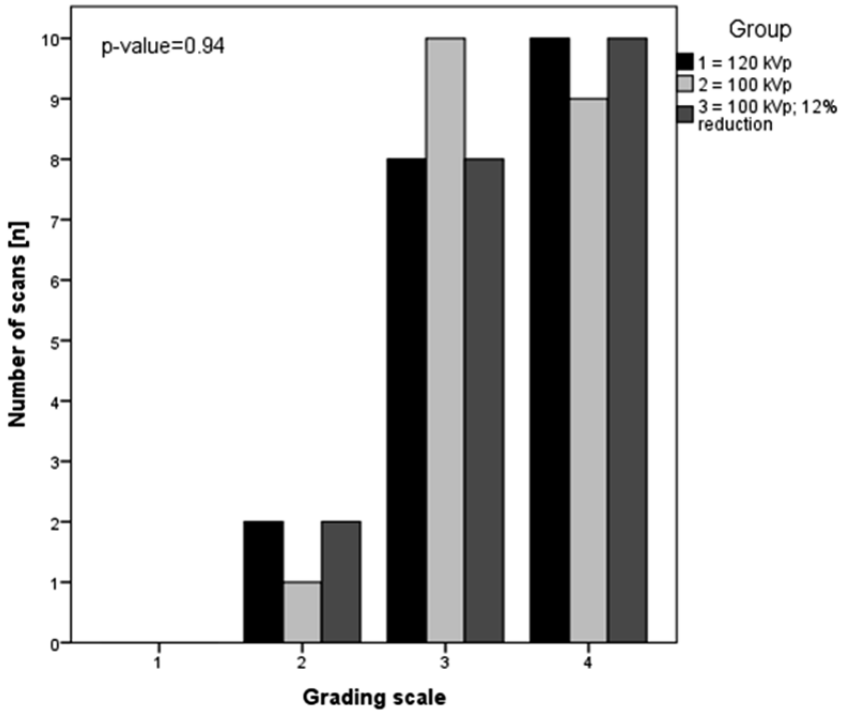

Figure 4.4 Subjective image qualities for group 1, 2 and 3
No significant differences were found between groups, with p=0.94 using Chi-square test. Grading scale: 1=non-diagnostic; 2=diagnostic with major artefacts; 3=good with minor artefacts and 4=excellent

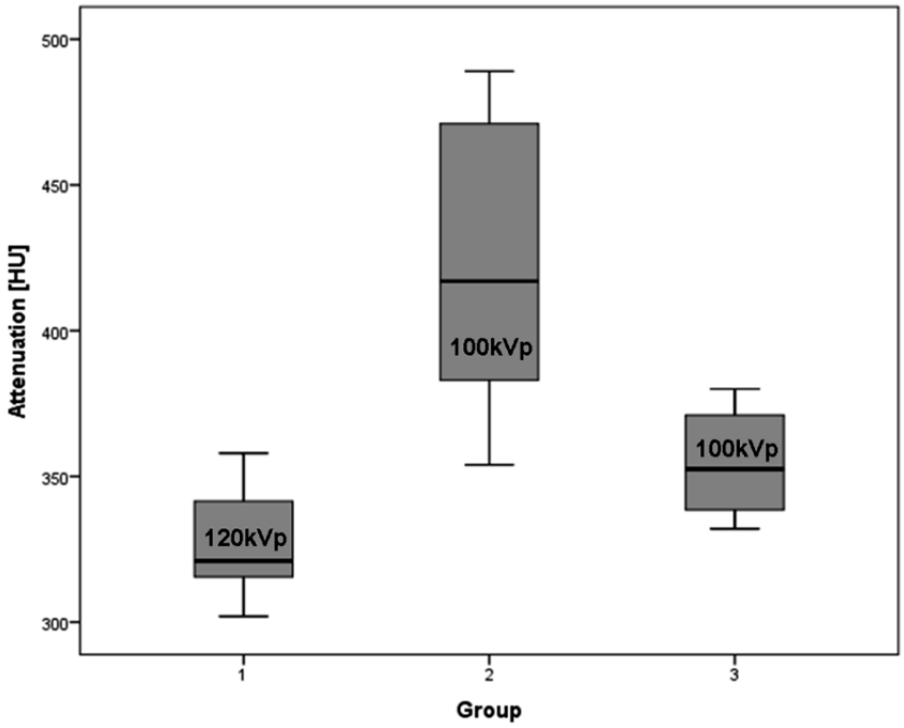

Figure 4.5 Box plots show mean enhancement levels in clinical setting for group 1, 2 and 3
12% reduction of injection parameters was used in group 3

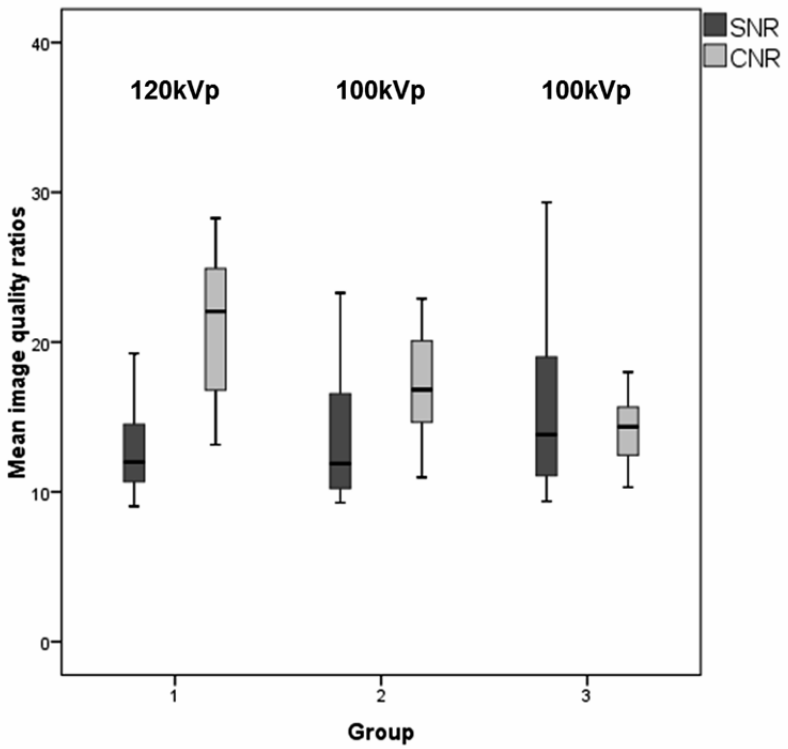

Figure 4.6 Box plots show the matching SNR and CNR in clinical setting for group 1, 2 and 3
12% reduction of injection parameters was used for group 3

DISCUSSION

The current study presents a systematic approach on how to optimise CM injection for CTA at lower kVp settings, with a target enhancement level of >325HU. The systematic approach was successfully applied in phantom settings and confirmed in a patient setup.

In the systematic approach CM could be reduced by 12-56% for different kVp settings and this is in line with other recent publications. For example, Lell *et al*[22] investigated kVp adjusted CM delivery in a systematic way for the thoraco-abdominal aorta with special regards to injection duration and IDR, using a porcine model. They also concluded that arterial enhancement could be maintained by adjusting the IDR to the specific kVp setting. They used a reduction percentage of 49% for 70 kVp which is almost in line with our results; however, they did not describe any results from a clinical setting.

Thor *et al*[23] investigated kVp adjusted CM volume reduction in various abdominal phantom sizes. They concluded that 44 – 53% CM volume could be saved using DSCT

with 80 kVp and 70 kVp, respectively. However, this was at the cost of radiation dose reduction: tube current was increased according to the kVp setting in order to maintain CNR. Namely, the challenge of reducing CM is to keep diagnostic image quality not only in terms of enhancement level but also in terms of CNR, as lower kVp settings result in higher image noise unless tube current could be adjusted sufficiently. Thus, the target level of 325HU would be sufficient only if image noise levels remained equal at all kVp settings. Unfortunately this is not possible for all type of CT scanners, hindering the use of lower kVp settings in a broad range of patients. Anyhow, modern CT scanners have higher tube current potential and better detector technology, allowing the use of lower kVp settings in a broader spectrum of patients and not only in pediatric patients and thinner patients.

In our clinical setting, we were able to apply 120 kVp and 100 kVp settings to patients weighing 73 – 90 kg while diagnostic image quality was maintained. The reduction to 100 kVp, including a CM volume reduction of 12%, was validated: attenuation values were diagnostic and comparable to those achieved in phantom, even with higher attenuation values for 100kVp settings compared to 120 kVp, which was probably due to a lower overall patient weight in group 3. This indicates that even higher CM reduction can be feasible in lower weight patients.
Adaptation of CM to lower kV settings has been investigated by other groups as well, even though mostly not in a systematic approach and lower kV settings had to be restricted to a certain weight group. Zhang *et al*[24] found that a reduction of CM and IDR by 10-20% in CCTA at 100 kVp as compared to 120 kVp yielded adequate diagnostic image quality in patients with mean body mass index (BMI) <25kg/m^2. LaBounty *et al*[25] used an 80 kVp protocol in patients with a BMI <25kg/m^2 undergoing CCTA, and found it to be feasible. However, CM parameters were not adapted, resulting in higher contrast enhancement with lower kVp, as well as overall attenuation values above 700 HU. These results emphasise the need for CM optimisation at different kVp settings in order to achieve the required enhancement level.
Kidoh *et al*[26] used an 80 kVp protocol for CTA in triple-rule out patients, achieving a 30% reduction of CM as compared to their standard protocol. Mean body weight was around 60 kg, however, which is not representative of the general patient population. Cao *et al*[27] used an 80 kVp protocol in patients undergoing CCTA, but only in patients with a BMI <23kg/m^2 and low calcium load. They also achieved a 30% reduction of CM volume but again only in a patient population not representative for the general population in terms of body weight (mean = 58 kg).

Practically, the use of lower kVp settings allow for the reduction of CM. However, as aforementioned, lower kVp settings without sufficient adjustment of tube current will result in higher image noise levels and therefore diagnostic image quality can be compromised. In most recent literature, several approaches of image reconstruction have

been explored to reduce image noise in low-dose CT while maintaining diagnostic image quality.[28-30] For example, Song *et al*[28] achieved a significant reduction of image noise and radiation dose by using IR (SAFIRE) in comparison to the use of FBP in contrast-enhanced CT examination of the liver. And Berlin *et al*[30] achieved comparable results by using hybrid IR compared to the use of FPB in contrast-enhanced pediatric abdominal CT.
Leng *et al*[29] used virtual monoenergetic dual energy (DE) CT images in combination with an energy domain noise reduction technique in water phantoms. An advantage of virtual monoenergetic images is that iodine attenuation increases at lower monoenergetic energy. From this study, they concluded that the use of the energy domain noise reduction algorithm substantially decreased image noise with lower monoenergetic settings.

The current study gives insight into the underlying principles of a standardised approach reducing the most important injection parameters at lower kVp settings (IDR and TIL). The results may promote understanding of how to apply lower kVp settings on an individual basis, how to directly link contrast parameters such as IDR and TIL to tube voltage, and how to subsequently optimise contrast and dose settings. In view of ongoing advancements in detector technology, especially in adaptation of tube-current-time product, the number of patients who will benefit from such an individualised approach can only be expected to increase in the future.[31-33]
Furthermore, the presented reduction percentages might be generalised to the imaging of other circulations – for example cerebral and peripheral CTA – as the reductions were adapted to the kVp setting and applied in relation to the standard injection protocol for the specific vasculature.

Limitations

Although the clinical applicability of the systematic approach in a circulation phantom was tested in patients, the number of patients was limited and clinical applicability of the 80kVp and 70kVp protocols was not tested due to technical limitations of the current scanner.

CONCLUSION

This study provides a unique description of a systemic approach to CM injection optimisation at different kVp settings. In a circulation phantom, lower kVp settings allowed a substantial reduction in CM volume - up to 56% at 70kVp - whilst maintaining diagnostically sufficient attenuation within the target vessels. Initial results in patients

confirmed this finding at 100kVp using 12% reduction of CM volume in CCTA. Attaining diagnostic attenuation values using reduced CM volumes may play an important role in the future – especially due to the ongoing advancements in detector technologies. Therefore, future prospective studies may help to define the clinical use of this technique in different circulations.

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CHAPTER 5

Individually tailored contrast enhancement in CT pulmonary angiography

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ABSTRACT

Purpose

The purpose was to evaluate individually shaped contrast media (CM) delivery in CT pulmonary angiography (CTPA) for suspected pulmonary embolism.

Materials and methods

100 consecutive emergency patients with clinical suspicion for pulmonary embolism were evaluated. High-pitch CTPA was performed on a 2nd generation dual-source CT using the following parameters: 100kVp, 200-250mAs$_{ref}$, rot.time 0.28s, 128x0.6mm col., image reconstruction 1.0/0.8mm (B30f). Group 1 (n=50) then received a fixed CM bolus (300mgI/ml, volume=90ml, flow rate=6ml/s); group 2 (n=50) received a body weight adapted CM bolus determined by dedicated contrast injection software. For analysis, groups were further subdivided into low (40-75kg) and high (76-117kg) weight groups. Technical image quality was graded using a four-point Likert scale (1=non-diagnostic; 2=diagnostic; 3=good and 4=excellent image quality) at the level of the pulmonary trunk and pulmonary arteries. Objective image quality analysis was done measuring contrast enhancement in Hounsfield units [HU] at the same levels. Attenuation levels >180HU were considered diagnostic.

Results

All examinations were graded diagnostic at each level. The individual minimum pulmonary attenuation was 184HU and 270HU for group 1 and 2, respectively. Mean attenuation was as follows: group 1: 475±105HU (40-75kg) and 402±115HU (76-117kg), $p<0.03$. Group 2: 424±76HU (40-75kg) and 418±100HU (76-117kg), $p=0.8$. For group 2, CM volumes were: 55±5ml (40-75kg) and 66±5ml (76-117kg), leading to a 16-51% CM reduction.

Conclusion

Even under emergency conditions, individualised CM protocols can provide diagnostic and robust image quality in CTPA for pulmonary embolism with a substantial reduction of CM volume for lower weight patients, compared to a fixed CM protocol.

INTRODUCTION

Pulmonary embolism (PE) is a major cause of morbidity and mortality with acute PE being the most severe clinical presentation.[1] Computed tomographic pulmonary angiography (CTPA) is widely used to rule out or confirm the presence of PE and is considered the reference standard for this emergency indication.[2, 3] The improvement of scanning techniques with the invention of the multidetector-row CT has led to high spatial and temporal resolution, better delineation of peripheral arteries and an increased detection rate of (sub-)segmental PE.[3, 4] Additionally, CTPA has been shown to provide an alternative diagnosis in up to 70% of patients where PE is not confirmed.[5] The diagnostic and clinical value of CTPA has already been firmly substantiated[5-8], thus future research should focus on optimising scan protocols and improving workflow.[9, 10] A considerable obstacle in current clinical practice is a substantial number of non-diagnostic scans, with reported rates ranging between 3.3% and 7.3%.[11, 12] However, for an emergency indication such as PE, the scan protocol should be expected to deliver robust and reliable results twenty four hours a day, seven days a week. According to current literature, a diagnostically enhanced CTPA requires an intra-arterial attenuation of at least 180HU, which allows for visualisation of pulmonary pathology in at least 90% of the patient population.[11, 13] The enhancement of pulmonary arteries depends on multiple factors: scan technique including tube settings (voltage [kVp]; current [mAs]), scan duration, patient related factors such as breathing (Valsalva) and body weight as well as contrast media (CM) administration parameters.[11, 14, 15] Regarding the latter, both the amount of iodine injected per second (iodine delivery rate; [IDR]) and the total amount of iodine (total iodine load; [TIL]) are important factors in the enhancement of the pulmonary arteries.[5, 14-16] One of the most influential patient related factors is body weight; arterial enhancement and body weight have been found to correlate significantly, as well as enhancement and body mass index (BMI).[14, 15] Therefore, fixed CM protocols may result in attenuation values below diagnostic level for heavier patients, whereas for skinny patients attenuation may exceed required levels. Therefore, a solution could possibly be found in individualising contrast application for each patient. This study aimed to prospectively evaluate individually shaped CM delivery in emergency CTPA for suspected PE.

MATERIALS AND METHODS

Ethics

A waiver of written informed consent was obtained from the local ethical committee (METC, ref. 14-4-198).

Study population

Inclusion criteria were: referral for CTPA for suspected PE; ≥18 years of age and a glomerular filtration rate ≥60ml/min/1.73m^2. All patients were weighed by radiological technicians directly before CTPA; in case of immobile patients weighing was sometimes obstructed and the last known weight was recorded from the electronic patient files, when available. Patients were excluded when an alternative scan protocol (e.g. higher kilovoltage; [kVp]) had to be used (n=11) or when body weight/injection data was incomplete (n=25). A total of 100 consecutive patients were included for data analysis.

Imaging protocol

All scans were performed on a 2nd generation dual-source multidetector-row CT scanner (Somatom Definition Flash, Siemens Healthcare, Forchheim, Germany) using a high-pitch CTA protocol (”Flash”) with a tube voltage of 100kVp, a tube current of 200-250mAs$_{ref}$ (CareDose 4D^{TM}, Siemens) and a pitch value of 2.6. A gantry rotation time of 0.28s and a slice collimation of 128x0.6mm were applied. Image reconstruction was performed using a medium-smooth soft tissue kernel (Siemens B30f) at a slice thickness of 1mm with an overlapping increment of 0.8mm.

CM injection protocol

Pre-warmed (37˚C [99˚F]) CM (Ultravist; Iopromide 300mgI/ml, Bayer Healthcare, Berlin, Germany) was used for all patients. CM was administered using a programmable dual-head CT injector (Stellant, Bayer), via an 18-20G intravenous injection catheter in the left or right antecubital vein.

The first fifty patients (group 1) received CM injection according to our clinical standard PE protocol consisting of a CM phase of 75ml, as well as a mixed phase with total 30ml of 50% CM and 50% NaCl (TIL: 27gI). Flow rate was 6ml/s (IDR: 1.8gI/s). All CM injections were followed by a saline chaser of 30ml at the same flow rate.

The second fifty patients (group 2) received individual CM injection protocols adjusted to body weight [kg] and scan duration [s], calculated by a dedicated contrast injection software (Certegra^{TM} P3T, Bayer). This injection software is able to calculate CM volume and flow rate based upon a nonlinear relationship between patient weight and duration of the CT data acquisition.[17,18] After the body weight of the patient and average scan duration for the specific acquisition are provided by the user, CM volume and flow rate will be adapted simultaneously in order to provide similar injection duration for each patient. All injections were followed by a saline chaser of 30ml at the same calculated flow rates.

For both groups, individual bolus timing in order to generate an individual start delay was performed using test bolus technique at the level of the pulmonary trunk: 20ml of CM were followed by 40ml of saline using the flow rates pre-calculated for the diagnostic scan. An overview of all injection parameters is listed in **table 5.1**.

Injection parameters	CM Bolus [ml]	Mixed phase* [ml]	Saline Chaser [ml]	Flowrate [ml/s]	TIL [gI]	IDR [gI/s]
Group 1	75	30	30	6.0	27	1.8
Group 2						
40-75kg	42-60	-	30	4.2-6.0	13-18	1.3-1.8
76-117kg	61-76	-	30	6.1-7.6	18-23	1.8-2.3

Table 5.1 Injection protocols as used in this study
For group 1 the injection protocol was fixed for all patients (n=50). In group 2 the injection protocol was adapted according to the patient weight in kg; this table shows the ranges of parameters that were used. *The mixed phase consisted of 50% CM and 50% NaCl

Clinical outcome

All images were immediately clinically evaluated by experienced radiologists. Information about the presence and location of PE was collected from the clinical reports.

Data processing

Acquired data was analysed on a dedicated medical workstation (SyngoVia^{TM}, Siemens) using 1mm transverse sections. Technical image quality of all scans was graded by an experienced research fellow (MK) who was blinded to the injection protocols, using a four-point Likert scale (1= non-diagnostic; 2= diagnostic; 3=good and 4=excellent image quality) at the level of the left and right pulmonary artery as well as at the level of lobular, segmental and sub-segmental arteries. Technical image quality was determined as a combination of contrast enhancement, image noise and the presence of artefacts.

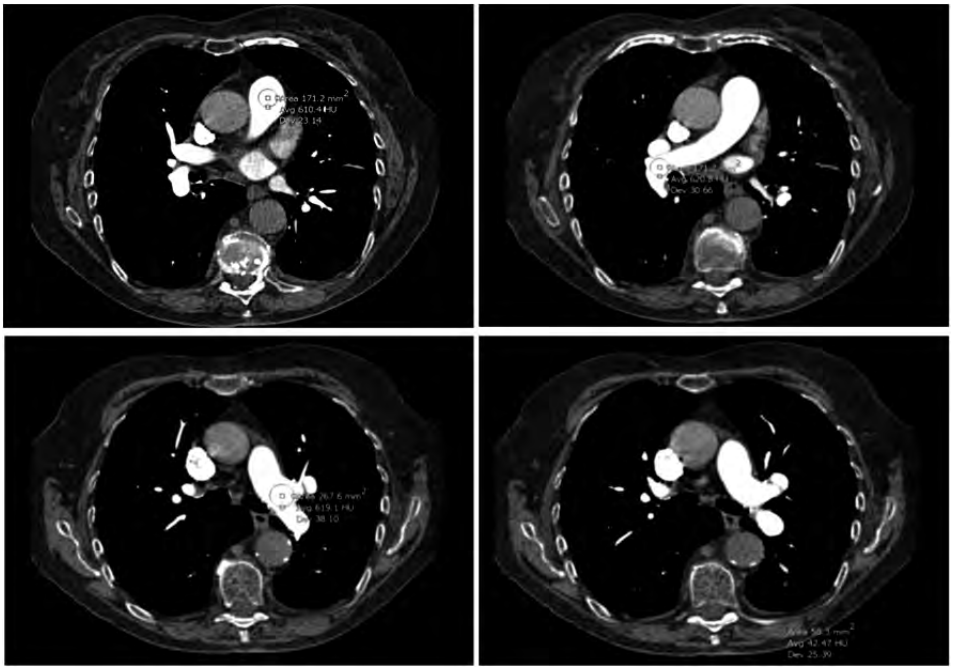

Figure 5.1 Images show the regions of interest (ROI) for attenuation measurements at level of the pulmonary trunk *(left top, 610HU*), right pulmonary artery *(right top, 620HU)*, left pulmonary artery *(left bottom 620HU)* and paraspinal muscle *(right bottom, 42HU)*

Objective image quality including contrast enhancement in Hounsfield units [HU], contrast-to-noise ratio (CNR) and signal-to-noise ratio (SNR) was measured by a research fellow (BH) who was blinded to the injection protocols. Regions of interest (ROIs) were manually delineated on the axial thin slices at the level of the origin of the pulmonary trunk just cranial to the pulmonary valve and in both left and right pulmonary artery (see **figure 5.1**). Sufficient image quality was defined as attenuation values >180HU and CNR values ≥ 10.[19] SNR and CNR were defined according to the following equations[13]: SNR = mean pulmonary enhancement (HU_{vessel}) divided by mean pulmonary enhancement standard deviation (SD_{vessel}). CNR = mean pulmonary enhancement (HU_{vessel}) minus mean muscle enhancement (HU_{muscle}) divided by mean muscle SD.
All injection parameters (volume, flow rate, peak flow rate and peak pressure) were continuously monitored by a data acquisition program (Certegra™ Informatics Platform, Bayer) and read out after each injection.

Statistical analysis

S Statistical analysis was performed using Statistical Package for Social Sciences version 22.0 (SPSS Inc, Chicago, IL, USA). For comparison between different body weights, patients were divided into two groups: 40-75kg (low weight) and 76-117kg (high weight). Groups were checked for normal distribution using the Kolmorov-Smirnov test. Continuous variables were reported as the mean ± standard deviation (SD) and differences between groups were calculated using one-way ANOVA with a Tukey test for post hoc comparisons. Categorical variables were reported as percentages and the chi-square test was used to measure differences between groups. All *p*-values are 2-sided, and a *p*-value below 0.05 was considered statistically significant.

RESULTS

Baseline characteristics

Baseline characteristics of the study population are summarised in **table 5.2**, no significant differences in baseline characteristics were found. For group 1 mean age [y], body weight [kg] and BMI [kg/m^2] were; 64±15 (range: 16-91), 75±17 (range: 49-109) and 26±5 (range: 18-39). For group 2 these values were 63±16 (range: 21-92), 71±15 (range: 43-117) and 25±5 (range: 15-39), with associated *p*-values of 0.79, 0.26 and 0.25, respectively.

Injection parameters

Mean flow rates in group 2 were 5.2±0.4ml/s for patients between 40-75kg and 6.1±0.4ml/s for patients between 76-117kg, ranging from 4.2 to 7.6ml/s. CM volumes were calculated as between 42ml (40kg) and 76ml (117kg), IDR ranged from 1.26 to 2.28gI/s, TIL from 12.6 to 22.8gI, respectively. Peak pressures for both groups ranged between 99±17psi and 122±33psi and did not differ significantly between group 1 and 2, with $p > 0.3$ (see **table 5.3**). Maximal injection pressure of 325psi was never reached in any patient or for any flow rate.

	Age [y]	Sex (Male; [%])	Body weight [kg]	Height [cm]	BMI [kg/m²]
Group 1	64±15	54	75±17	169±9	26±5
Group 2	63±16	46	71±15	170±8	25±5
p-value	0.79	0.42	0.26	0.82	0.25

Table 5.2 Baseline characteristics
This table shows baseline characteristics of the two main groups; no significant differences were found

		Flow rate [ml/s]	Peak Flow rate [ml/s]	IDR [gI/s]	Main bolus volume [ml]	TIL [gI]	Iodine per kg [gI]	Peak Pressure [psi]
Group 1	Low weight 40-75kg	5.8±0.3	6.3±0.0	1.8±0.0	89.5±1.1	26.8±0.3	0.43±0.05	103±18
	High weight 76-117kg	5.7±0.1	6.3± 0.0	1.8±0.0	90.0±0.3	26.9±0.1	0.30±0.03	106±26
Group 2	Low weight 40-75kg	5.2±0.4	5.8±0.5	1.6±0.1	54.6±4.5	16.4±1.4	0.26±0.05	99±17
	High weight 76-117kg	6.1±0.4	7.0±0.5	2.0±0.1	65.6±4.7	19.7±1.4	0.20±0.00	122±33
p-value		<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	0.33

Table 5.3 Injection parameters for both groups
A significant decrease is seen for total iodine load (TIL), main bolus volume and iodine per kg for the individualised protocol versus standard protocol, in both low and high weight group

TIL was 27gI for group 1 and ranged from 12.6gI to 22.8gI in group 2. The mean TIL for group 2 was 16±1.4gI (40-75kg) and 20±1.4gI (76-117kg), showing a significant CM dose reduction for all patients compared to group 1, with $p<0.01$ (see **table 5.3** and **figure 5.2**). In patients who received an individualised bolus, CM volume could be reduced by 51%, 33% and 16% for the lightest patient of group 2 (44ml at 42kg), an average patient (60ml at 75kg) and the heaviest patient of group 2 (76ml at 117kg), respectively.

For both weight groups the iodine per kg body weight was significantly lower in group 2, with $p<0.01$. Iodine per kg body weight in group 1 was: 0.4gI/kg for 40-75kg and 0.3gI/kg for 76-117kg patients. For the same weight groups values in group 2 were 0.3gI/kg and 0.2gI/kg respectively (see **table 5.3** and **figure 5.3**).

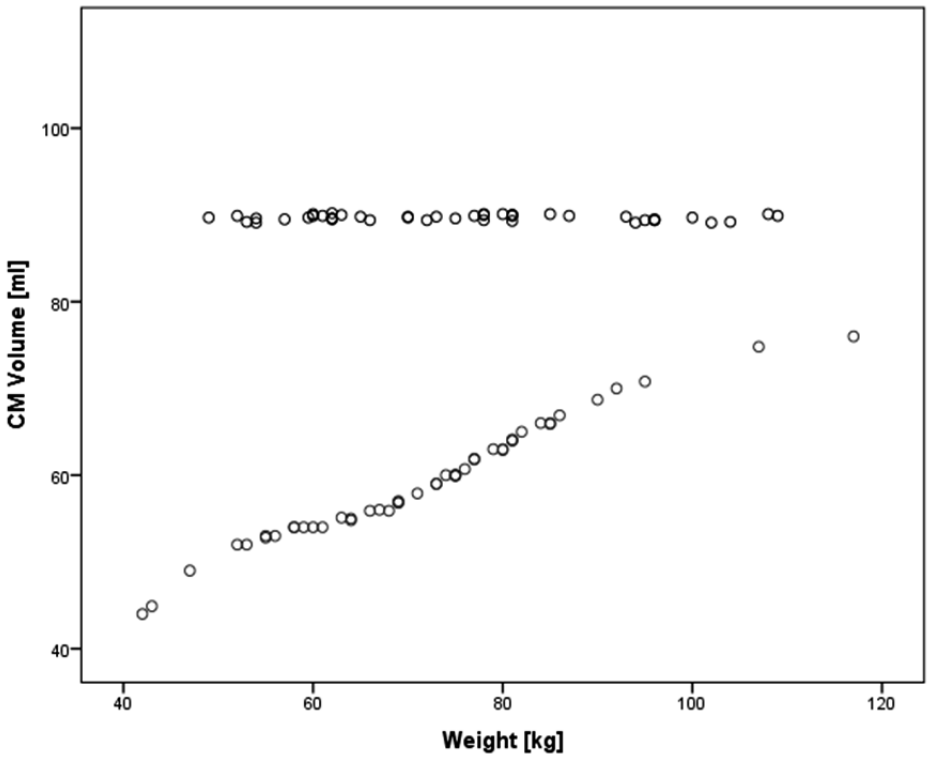

Figure 5.2 Scatter-dot shows all patients by weight in kilograms with their corresponding received CM volume
All group 1 patients received 90ml CM. All patients in group 2 received less CM (range: 44-76ml) and for low weight patients the CM dose reduction was most pronounced

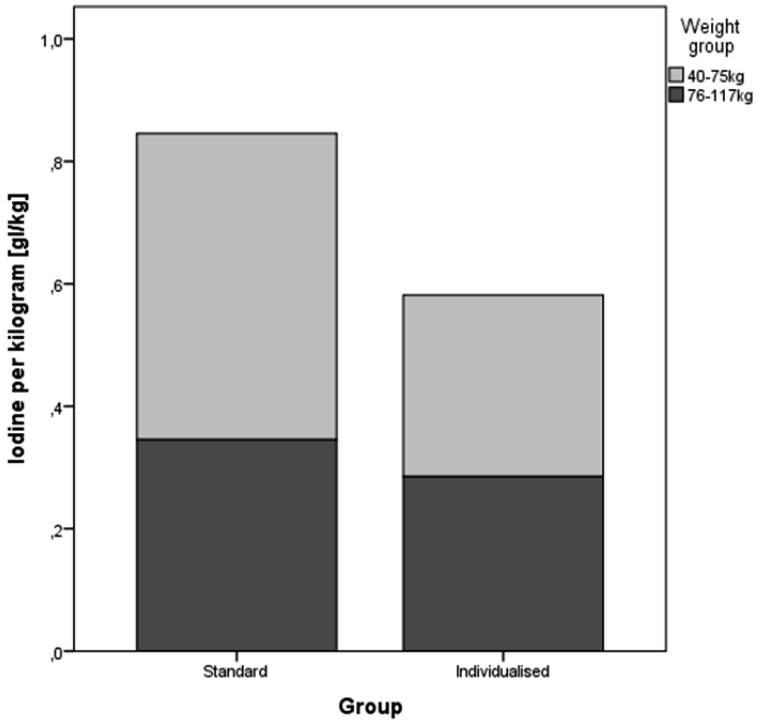

Figure 5.3 This bar graph shows the mean iodine per kg load for the low weight and the high weight patients in group 1 (left) and group 2 (right)
The iodine per kg is reduced for group 2 both in low and high weight categories

Clinical Outcome

The total incidence of PE in this study population was 18%. In group 1 a total of 10 patients was diagnosed with PE, including 2 central, 3 lobar and 5 segmental emboli. Group 2 showed 8 patients with PE; 2 patients had lobar PE, 3 had segmental and 3 had sub-segmental PE. These are the most proximal points of the emboli, for an overview of the extent of disease in each patient see **table 5.4**.

Technical image quality

For both groups, all scans were graded as diagnostic image quality at each anatomic level. Lowest grade was 2 and this grade was found in one patient of each group, only. All other scans were graded as 'good' or 'excellent' at each anatomic level.

	Standard										Individualised							
Central			X	X	X													
Lobar		X	X	X	X		X								O			O
Segmental	X	X	X	X		X	X	X	X	X	O			O	O	O	O	O
Subsegmental		X	X	X		X	X	X				O	O	O	O	O	O	O

Table 5.4 Extension of PE in each group
Each column represents one patient and the extent of disease found. 18 patients showed PE, with n=10 in group 1 and n=8 in group 2

Objective image quality

For group 1, mean attenuation values in the pulmonary trunk (PT) and in the right and left pulmonary artery (RPA/LPA) were as follows (40-75kg vs. 76-117kg): 475±105HU vs. 402±115HU (PT); 435±94HU vs. 369±104HU (RPA) and 426±101HU vs. 360±102HU (LPA). There was a significant difference in attenuation values between weight groups for PT, LPA and RPA, with *p*-values of 0.03 (see **table 5.5**). For group 2, these attenuation values were as follows (40-75kg vs. 76-117kg): 424±76HU vs. 418±100HU (PT); 418±84HU vs. 408±90HU (RPA) and 413±81HU vs. 403±92HU (LPA). Within group 2, no significant differences were found in attenuation values between both weight groups, all *p*-values >0.6 (see **table 5.5**).

		PT [HU]	RPA [HU]	LPA [HU]	CNR	SNR
Group 1	Low weight 40-75kg	475±105	435±94	426±101	15±5	14±4
	High weight 76-117kg	402±115	369±104	360±102	11±5	11±3
p-value		0.03	0.03	0.03	>0.01	>0.01
Group 2	Low weight 40-75kg	424±76	418±84	413±81	16±6	15±5
	High weight 76-117kg	418±100	408±90	403±92	15±5	13±3
p-value		0.80	0.67	0.70	0.24	>0.01

Table 5.5 Mean pulmonary artery attenuation values
Mean attenuation values for low and height weight groups per injection protocol and per artery, comparing a low weight and a high weight group

On a group level, no significant differences in attenuation values were found between group 1 and 2. However, attenuation values for group 2 show a much smaller range (see **figure 5.4** and **5.5**). Both groups showed no non-diagnostic scans with a minimum mean pulmonary attenuation of 184HU for group 1 and 270HU for group 2.
CNR was acceptable for both groups, but better for group 2, with values (low weight - high weight) of 16±6 and 15±5 vs. 15±5 and 11±5. SNR values for group 1 were 14±4 (low weight) and 11± 3 (high weight), for group 2 these values were 15± 5 and 13± 3, respectively (see **table 5.5**).

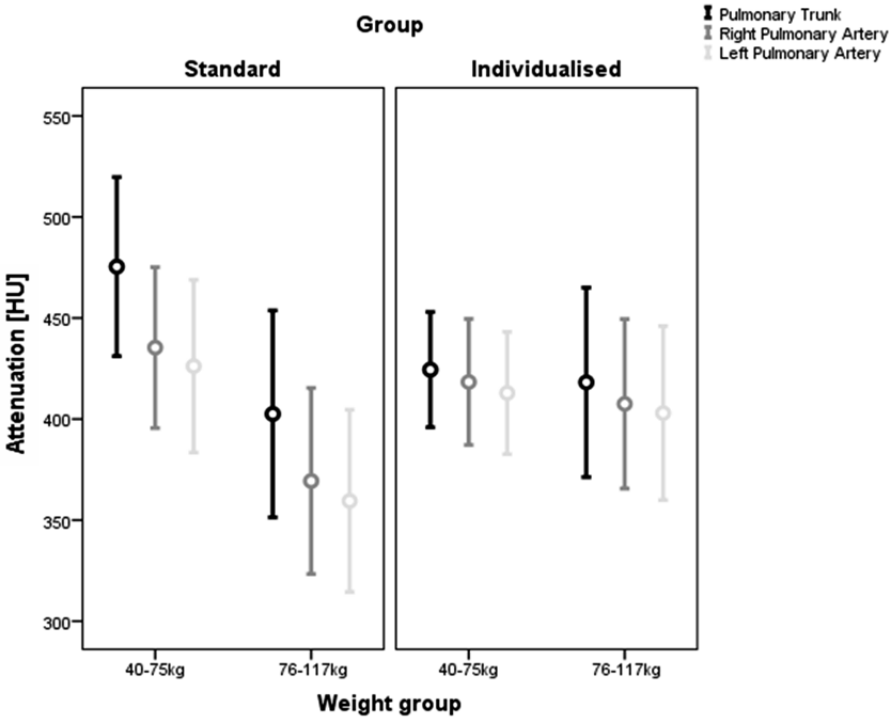

Figure 5.4 Error bars show the mean attenuation and 95% confidence intervals for both injection protocols and weight groups

The intervals define the values that are most plausible for the mean of a greater population. A decreased mean attenuation was seen for the higher weight group within the standard protocol *(left)* and similar mean attenuation was seen for both weight groups within the individualised protocol *(right)*

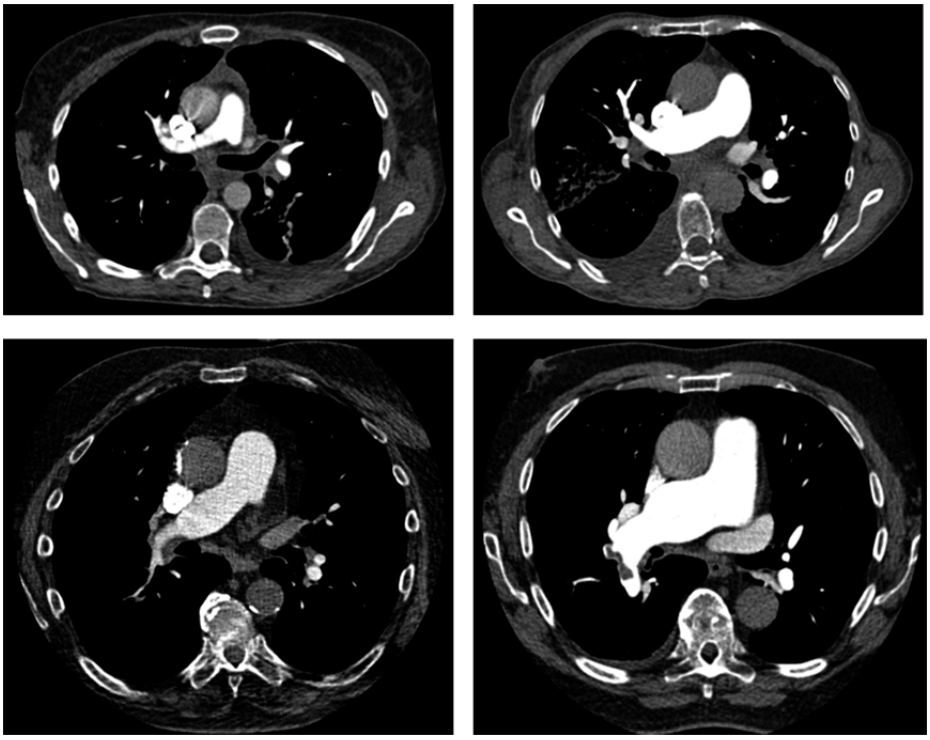

Figure 5.5 Images show contrast enhancement at the level of the pulmonary trunk (W-C levels: 600-125) Left images show two patients from group 1 including low weight *(top)* and high weight *(bottom)* with attenuation values of 532HU and 362HU respectively. Right images show two patients from group 2 including low weight *(top)* and high weight *(bottom)* with attenuation values of 555HU and 520HU respectively. Right bottom image also shows right lobar PE

DISCUSSION

Individualised CM bolus administration in CTPA provided equal to superior enhancement compared to a fixed protocol whilst using less CM volume. Moreover, greater consistency of vascular enhancement values – indicating a more reliable and robust protocol – was observed throughout group 2, whereas the scans for group 1 showed a steady decline in attenuation with increasing body weight. The observed homogeneity of attenuation throughout all patient weights is concordant with other studies using CM individualisation in CTA, however this research shows an additional reduction of CM volume as well.[17, 20]

Some studies on bodyweight adapted CM protocols for CTPA in selective, low weight patient groups have been published: Holmquist *et al* used an 80kVp protocol with TIL of around 13gI in a low weight patient group and Kristiansson *et al* reduced the TIL in a similar patient group even further to 9.6gI. However, 8-12% of the examinations were

regarded as suboptimal.[21, 22] In coronary CTA a smaller SD of intracoronary attenuation was reported when using a body weight adapted injection protocol, indicating a smaller variation in attenuation values between individual patients.[17, 20]

In CTPA the lower HU limit is important as CM attenuation is typically even lower in the more peripheral arteries. A CTPA with arterial attenuation below 180HU may be considered to be of non-diagnostic quality to reliably detect subsegmental emboli as mean HU values for acute and chronic embolism are around 33HU and 87HU, respectively.[23] In this study all patients met this crucial cut-off value of 180HU.

CNR was sufficient in both groups. CNR values above 10 are generally accepted in coronary CTA literature[19], however there is currently no consensus regarding CNR values in CTPA. In this study, CNR decreased significantly with increasing patient weight in group 1, whereas CNR remained constant in the group with individualised CM injections (group 2). The observed decrease in CNR can be attributed to lower CM attenuation values in heavier patients in combination with higher image noise due to higher body mass.[19, 24] A further improvement in CNR could be achieved by alteration of reconstruction methods, for example with the implementation of iterative reconstruction (IR).[25-27] However, subjective image quality will not always be experienced as superior due to possible loss of contrast between different densities.

All patients (up to 117kg) from the individualised CM group received less CM compared to standard group patients. The original fixed protocol in this study used a broad CM bolus (injection over 20s) with a relatively high flow rate (IDR of 1.8gI/s), which had been chosen as a safe option. The problems regarding the realisation of diagnostic quality in CTPA previously called for a safe 'one size fits all' bolus, in order to prevent double scanning and bolus administration. Consequently, part of the CM reduction in the individualised group can be traced back to the comparison with a generous fixed CM bolus. Nevertheless, even attenuation in patients weighing 76-117kg from the individualised group was higher compared to patients of equal body weight in the standard group. The use of relatively smaller CM volumes in combination with higher flow rates indicates an inferior importance of CM volume and TIL compared to flow rate and IDR with respect to arterial enhancement, even under emergency conditions: IDR can be manipulated by adjusting either flow rate or iodine concentration of CM (IDR [gI/s] = flow rate [ml/s] x iodine concentration [gI/ml]). Some authors state that attenuation in CTA could be increased by using higher iodine concentrations of CM[28], whereas others state that increasing IDR – by increasing flow rate – is the most influencing factor regarding CM enhancement.[16, 29] Increasing flow rate might be preferable for optimising CM application for CTA, since increasing iodine concentration of CM simultaneously increases CM viscosity. A phantom study conducted by Kok *et al* showed that low concentration, low viscosity and pre-warmed CM are beneficial for achieving low injection pressures.[30]

Nowadays, contrast induced nephropathy (CIN) might not be as much of a concern as previously suspected.[31, 32] However, Lee *et al* found thyroid dysfunction in 22% of pa-

tients after a single iodinated CM injection, with urinary iodine excretion correlating to the TIL.[33] According to a recent review contrast-induced thyroid dysfunction mostly appears to be transient, however there is a risk for complications.[34] The precise relationship between CM volume and thyroid dysfunction remains unclear to this point, thus administering smaller volumes of CM might prove a safe option and help to avoid delays in scheduling CTPA. Furthermore, smaller bolus volumes in other CTA protocols have been shown to reduce costs in medical clinics.[35]

With the current scan protocol a tube voltage of 100kVp was used. Already some advancements have been made using lower kVp settings in CTA.[25-27, 36-38] A decrease in kVp increases intra-arterial CM attenuation, because the higher photon energy at lower kVp settings is closer to the iodine k-edge of keV.[4, 24, 39, 40] Many studies focused on low kVp protocols, however one must ensure to concordantly increase mAs to avoid excessive image noise.[19, 41, 42] For future optimisation it may prove beneficial to further define the optimal IDR values and CM volumes per weight category that ensure a mean attenuation of 180-300HU for all kVp settings regularly used in the clinics, e.g. 120kVp, 100kVp and 80kVp.

Limitations

For this study a dedicated scan protocol at 100kVp was used, only. This resulted in exclusion of patients with body weights requiring higher kVp protocols, e.g. 150kg body weight at 120kVp.

CONCLUSION

The use of individualised CM protocols provides diagnostic and robust enhancement in emergency CTPA, as well as a substantial CM volume reduction in lower weight patients, compared to a fixed CM protocol.

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CHAPTER 6

Low contrast media volume in pre-TAVI CT examinations

Kok M, Turek J, Mihl C, Reinartz SD, Gohmann RF, Nijssen EC, Kietselaer BLJH, Kats S, van Ommen VG, Wildberger JE, Das M.
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ABSTRACT

Purpose

To evaluate image quality using reduced contrast media (CM) volume in pre-TAVI assessment.

Materials and methods

47 consecutive patients referred for pre-TAVI examination were evaluated. Patients were divided into two groups: group 1 BMI<28kg/m^2 (n=29); and group 2 BMI>28kg/m^2 (n=18). Patients received a combined scan protocol: retrospective ECG-gated helical CTA of the aortic root (80kVp) followed by a high-pitch spiral CTA (group 1: 70kVp; group 2: 80kVp) from aortic arch to femoral arteries. All patients received one bolus of CM (300mgI/ml): group 1: volume=40ml; flow rate=3ml/s, group 2: volume=53ml; flow rate=4ml/s. Attenuation values [HU] and contrast-to-noise ratio (CNR) were measured at the levels of the aortic root (helical) and peripheral arteries (high-pitch). Diagnostic image quality was considered sufficient at attenuation values ≥200HU and CNR ≥3.

Results

Diagnostic image quality for TAVI measurements was obtained in 46 patients. Mean attenuation values and CNR (HU±SD) at the aortic root (helical) were: group 1: 381±65HU and 13±8; group 2: 442±68HU and 10±5. At the peripheral arteries (high-pitch), mean values were: group 1: 430±117HU and 11±6; group 2: 389±102HU and 13±6.

Conclusion

CM volume can be substantially reduced using low kVp protocols, while maintaining sufficient image quality for the evaluation of aortic root and peripheral access sites.

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is considered an effective treatment option for patients with severe and symptomatic valve stenosis not suitable for conventional valve replacement.[1, 2] Throughout the years, multi detector-row CT (MDCT) has become the standard non-invasive imaging method in pre-TAVI assessment for aortic root dimensions and access site.[3, 4] To ensure technical success and optimal valve-prosthesis sizing, dedicated scan technique including reliable contrast media (CM) injection protocols during pre-operative imaging are of utmost importance. However, the CM required may pose a risk for TAVI candidates, who are frequently suffering from impaired renal function and considered to be at increased risk of contrast-induced nephropathy (CIN).[5, 6] The European Society of Urogenital Radiology (ESUR) guidelines recommend expansion of extracellular volume as one of the measures to prevent CIN.[7] However, aortic stenosis in TAVI candidates does not allow for fluid expansion due to the increased risk of subsequent heart failure.

Not only pre-existing renal insufficiency is correlated with increased risk of CIN, but also the use of increased CM volume[8] as well as the administration of multiple doses of intravascular CM within a short period of time (<24 hours).[9, 10]

TAVI protocols – as described in the literature – usually entail the injection of large CM volumes up to 120ml to ensure optimal filling of the aortic root as well as the peripheral arteries.[4, 11-13] In the combination of ultra-fast data acquisition and use of low kVp protocols, this amount might be substantially reduced, offering patient tailored CT protocols.

Thus, the aim of this study was to evaluate the use of low CM volumes in pre-TAVI CT examinations, using low kVp settings in combination with iterative reconstruction techniques.

MATERIALS AND METHODS

Ethics

A waiver of written informed consent was obtained from the local ethical committee (METC, ref. 14-4-165).

Patient population

Between July 2014 and January 2015, 56 consecutive patients with severe symptomatic aortic stenosis were evaluated. All of them were referred from the cardiology outpatient department for pre-interventional assessment of aortic root dimensions and peripheral arteries. Patients with body mass index (BMI) >35kg/m^2 received a diver-

gent scan protocol and were therefore excluded (n=9). The other 47 patients received a specific scan and injection protocol according their BMI: Group 1 BMI <28kg/m^2; (n=29); Group 2 BMI >28kg/m^2 (n=18).[14, 15]
Other patient characteristics such as age, gender, height and weight were recorded.

MDCT scan protocol

All examinations were performed on a 2nd generation dual-source CT scanner (Definition Flash; Siemens Healthcare, Forchheim, Germany). Aortic root dimension assessment was carried out using a retrospective ECG-gated helical scan in caudo-cranial direction with parameters as follows: tube voltage 80kVp; effective tube current 370mAs_{eff}; rotation time 0.28s; slice collimation 128x0.6mm; pitch value 0.23. Tube current was set to 370mAs_{eff}, being the highest possible value for this scan protocol using this type of scanner. Image reconstruction of the entire cardiac cycle was done at the 20% phase of the cardiac cycle with individually adapted field of view (FOV) at 0.6mm slice thickness, an increment of 0.4mm using raw-data based iterative reconstruction (kernel I26f, SAFIRE [Sinogram Affirmed Iterative Reconstruction], strength 3).
Directly afterwards, all patients received a non ECG-triggered high-pitch spiral scan (flash) of the aorta in cranio-caudal direction from the aortic arch to the femoral arteries (see **figure 6.1**). Scan parameters were as follows: reference tube-current-time product 400mAs_{ref}; rotation time 0.28s; slice collimation 128x0.6mm; pitch value 3.0. Scan protocol varied for the two groups in tube voltage setting - group 1 at 70kVp, group 2 at 80kVp - and effective tube current was 90-122mAs_{eff} (maximum possible values were 93 and 122mAs_{eff} for 70 and 80kVp, respectively). Images were reconstructed with individually adapted FOV at 2mm slice thickness with an increment of 1.4mm using an I30f kernel (SAFIRE, strength 3 - see **figure 6.2**). Dose modulation (CAREDose4D, Siemens) was used. In **table 6.1** all relevant scan parameters are summarised. Total scan time of the combined acquisition was 13-14s: 6-7s for retrospective ECG-gated acquisition, 5s gap between acquisitions and 2s for the high-pitch acquisition. In order to minimise the gap between acquisitions, the scan direction was adapted accordingly, starting with a caudo-cranial direction for the helical scan, followed by a cranio-caudal direction for the high-pitch spiral scan.

Protocol	Cardiac	Aorta
Mode	Spiral	High pitch
Collimation [mm]	0.6	0.6
Acquisition [mm]	128*0.6	128*0.6
Tube voltage [kVp]	80	70/80 (group 1/group 2)
Dose modulation	off	on
Tube current [mAs] mAs_{ref} mAs_{eff}	 370 370	 400 90-122
Rot.Time [s]	0.28	0.28
Pitch	0.23	3.0
Delay [s]	Test bolus technique	Test bolus technique
Scan time [s]	6-7	2
Direction	Caudo-cranial	Cranio-caudal
Reconstruction Slice thickness [mm] Increment [mm] Kernel	Best Systolic – 20% 0.6 0.4 I26f	 2.0 1.4 I30f

Table 6.1 Scan protocol parameters of both helical and high-pitch acquisitions

CM injection protocol

Monomeric, non-ionic, low-osmolar iodinated CM (300mgI/ml; Iopromide; Bayer Healthcare, Berlin, Germany) was prewarmed to standardised 37°C prior to injection in the antecubital vein using catheter sizes between 18-22G (Sterican, Braun, Melsungen, Germany). Group 1 received a CM bolus of 40ml followed by a saline flush of 36ml, both at injection rate 3ml/s. Group 2 received a CM bolus of 53ml followed by a saline flush of 48ml, both at injection rate 4ml/s. Injection time of CM bolus and saline flush was kept constant in both groups (CM bolus: 13.3; saline flush: 12s). Total iodine load (TIL, [gI]) and iodine delivery rate (IDR, [gI/s]) were kept constant at 12g and 0.9gI/s for group 1; as well as 15.9g and 1.2gI/s for group 2. In order to determine time to peak (TTP) for accurate scan delay settings, test-bolus technique was used with 10ml undiluted CM followed by 30ml saline, injected at 3ml/s or 4ml/s for group 1 and 2, respectively. Injection parameters such as injection pressures [psi], flow rates [ml/s] and total amount of CM [ml] were continuously monitored by a data acquisition program (Certegra™ Informatics Solution, Bayer) and read out after each injection.

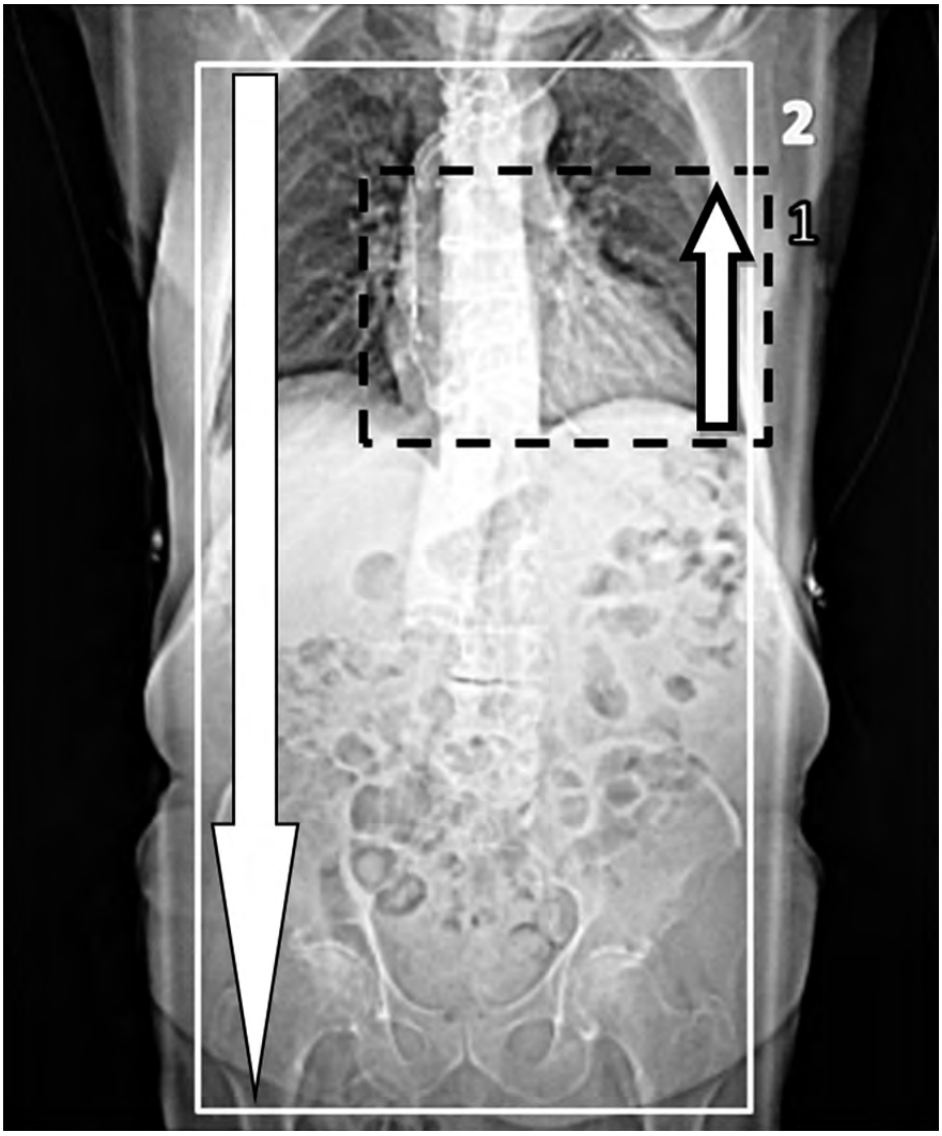

Figure 6.1 This figure shows the scout view with the planned anatomical range
The box with the dashed lines (1) indicates the retrospective ECG-gated acquisition of the heart in caudo-cranial direction. Box 2 indicates the high-pitch acquisition from the aortic arch to the femoral arteries in cranio-caudal direction

Quantitative analysis

Radiation dose

The dose-length product (DLP) was recorded for each protocol to calculate the effective dose [mSv]. The effective dose (E) was quantified by multiplying the DLP value and the combination of conversion coefficients (k) of chest (k = 0.014 mSv/[mGy.cm]), abdominal (k = 0.015 mSv/[mGy.cm]) and pelvic (k = 0.017 mSv/[mGy.cm]).[16] Because of the thoracic-abdominal-pelvic scan range, an average conversion factor (k = 0.015 mSv/[mGy.cm]) was used.[16]

Image quality

Image analysis was performed of both helical and flash scans. For the helical scan, the 20% time point of cardiac cycle was used for image quality assessment.[17] Quality determination was based on the ability of images to provide diagnostically sufficient information of the aortic root (annulus and root diameters, distance from annulus to coronary ostia and length of valve leaflets) and aorto iliofemoral arteries for dimensional measurements (iliofemoral diameter). The latter is as well as tortuosity, calcifications and/or atherosclerosis part of the access assessment.[18] Image quality was determined from a combination of arterial enhancement, image noise and presence of artefacts.

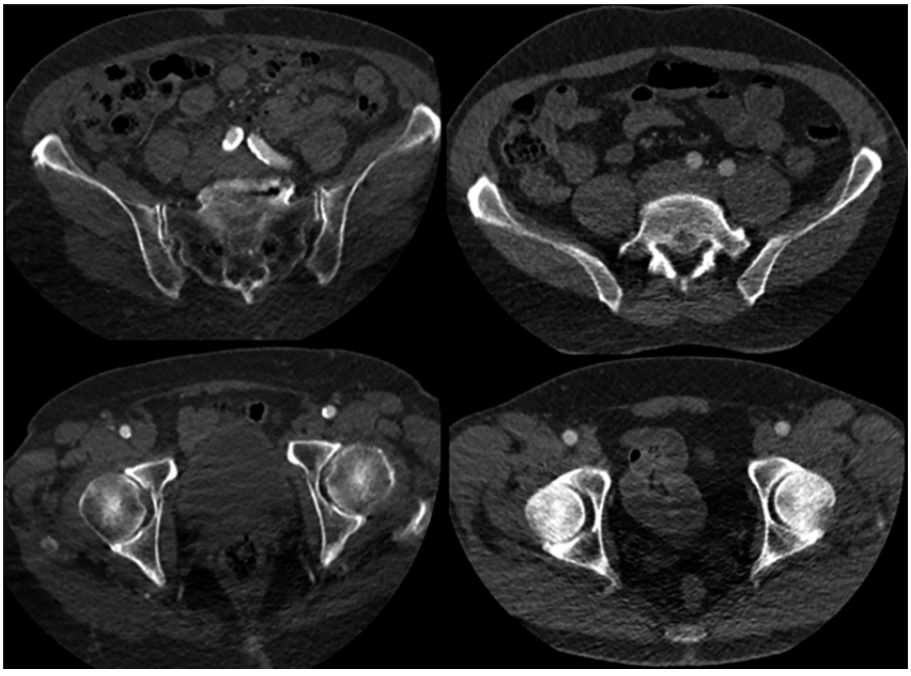

Figure 6.2 Images show the iliofemoral arteries obtained by the high-pitch CTA
Images were obtained using 80kVp *(left)* and the 70kVp *(right)*

Objective image quality measurements were performed by two experienced observers in consensus: attenuation in the region of interest (ROI), signal-to-noise ratio (SNR), and contrast to noise ratio (CNR). Circular ROIs (as large as possible) were placed at six levels of the aorta. The ascending aorta (AA) was evaluated from both the 80kVp helical scan and the 70/80kVp high-pitch spiral scan. The other five levels of the aorta (aortic arch [arch]; descending aorta [DA]; abdominal aorta [AAo]; right and left common iliac arteries [RCIA and LCIA] and right and left common femoral arteries [RCFA and LCFA]), were evaluated from the 70/80kVp high-pitch spiral scan, only.
SNR was defined as vessel enhancement in Hounsfield Units [HU] divided by vessel enhancement standard deviation (SD). CNR was defined as vessel enhancement (HU_{vessel}) minus adjacent muscle tissue enhancement (HU_{muscle}), divided by adjacent muscle tissue enhancement SD. Diagnostic image quality was considered sufficient at attenuation values >200HU[19, 20] and CNR >3.[21]
Subjective image quality (IQ) of both the helical and the high-pitch acquisition was determined by rating the presence of artefacts using a 4-point grading-scale: 1=non-diagnostic image quality; 2=significantly reduced image quality due to major artefacts, but still diagnostic for assessment; 3=good image quality with minor artefacts and 4=excellent image quality without artefacts.
Images were analysed using multiplanar reformation (MPR) with Syngo-Via™ software (Siemens).

Renal function
For the evaluation of renal function of this population, estimated glomerular filtration rate (eGFR; [ml/min/1.73m^2]) and serum creatinine [µmol/L] ≤12 months before the pre-TAVI CT scan were recorded according to the current hospital protocol.
Long-term renal function was evaluated by recording eGFR values ≥1-2 months after CTA.

TAVI procedure
For the evaluation of the placement of the valve prosthesis, the amount of patients treated by TAVI was recorded, as well as the survival rate after one month post TAVI. In addition, the CT measurements from the radiological reports were compared to the actual size of the valve prosthesis. References proposed guidelines show best results when using area derived diameter or mean diameter for valve sizing.[4, 22] For both balloon-expandable prosthesis and self-expandable prosthesis oversizing was recommended, by 10-15%.

Statistical analysis

Data analysis was conducted using SPSS version 20.0 (SPSS Inc, Chicago, IL, USA). Continuous variables were reported as mean±SD, categorical values as proportions [%]. The chi-square test was used to measure differences between categorical variables. Continuous variables were compared using independent-samples t-test or ANOVA test. In addition, post hoc comparisons of differences between the vascular segments were performed. All reported p-values are 2-sided, and a p-value of less than 0.05 is considered statistically significant.

RESULTS

Baseline characteristics

Baseline characteristics are listed in **table 6.2**. Group 1 consisted of 16 males and 13 females with average age 76±9y and BMI 22±3kg/m^2. Group 2 consisted of 5 males and 13 females with average age 75±9y and BMI 31±2kg/m^2.

Baseline characteristics	Group 1 (n=29)	Group 2 (n=18)	P-value
Age [y]	76±9	75±9	0.78
Gender [male]	16 [55%]	5 [28%]	0.07
Height [cm]	171±9	166±10	0.08
Weight [kg]	67±11	85±12	<.001
BMI [kg/m^2]	22±3	31±2	<.001
eGFR [ml/min/1.73m^2]			
Before CT[a]	54±8 (35 - 60)	55±8 (36 - 60)	0.65
After CT[b]	57±4 (46 - 60)	57±6 (42 - 60)	0.95

Table 6.2 Baseline characteristics
BMI = Body mass index; [a] <1 year before CTA; [b] ≥1-2 months after CTA

Radiation dose and CM injection

Radiation dose- and CM injection parameters are given in **table 6.3**. Mean effective radiation dose for the combined scans was lower for group 1 (6±2mSv) as compared to

group 2 (8±2mSv); *p*=0.06. Effective dose for helical and high-pitch scans were respectively 5±1mSv and 0.9±0.1mSv for group 1, and 6±1mSv and 1.8±0.2mSv for group 2. Mean volume, flow rate, peak flow rate, and peak pressure for group 1 and group 2 were: 40.0±0.1ml and 53.0±0.1ml; 2.9±0.0ml/s and 3.9±0.1ml/s; 3.4±0.0ml/s and 4.2±0.0ml/s; 54±8psi and 68±8psi respectively.

Radiation dose parameters	Group 1 (n=29)	Group 2 (n=18)	P-value
Total $CTDI_{vol}$ [mGy]	40±9	38±9	0.38
Total DLP [mGy.cm]	443±135	521±124	0.06
Total Effective Dose [mSv] *Helical* *High-pitch*	6±2 5±1 0.9±0.1	8±2 6±1 1.8±0.2	0.06 0.30 <.001
CM injection parameters			
Applied volume [ml]	40.0±0.1	53.0±0.1	<.001
Applied flow rate [ml/s]	2.9±0.0	3.9±0.1	<.001
Peak flow rate [ml/s]	3.4±0.0	4.2±0.0	<.001
Peak pressure [psi]	54±8	68±8	<.001

Table 6.3 Radiation dose and injection related parameters
Values are expressed as mean±SD

Image quality

Of the image sets obtained from 47 patients, 46 were diagnostically sufficient for aortic root anatomy, cardiac structures, and aorto iliofemoral anatomy. In one patient image quality was insufficient; this was due to streak artefacts caused by bilateral prosthesis material at the level of the hips and therefore at the level of the femoral arteries. Prosthesis material was present in one other patient (right hip) and femoral access could be properly depicted in this patient.

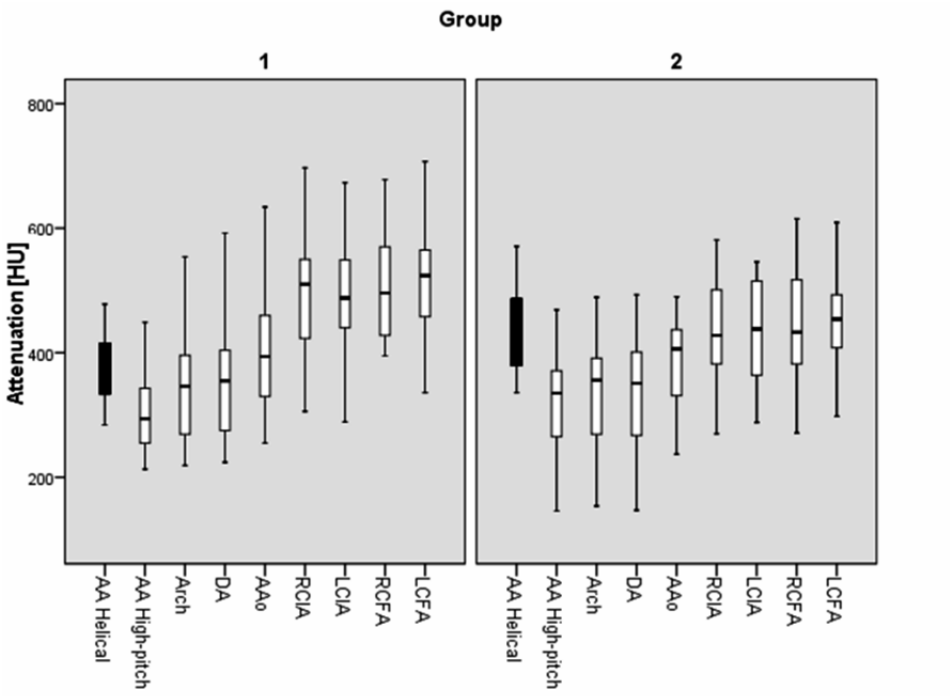

Figure 6.3 Box plots showing attenuation levels of each vascular segment
''AA helical'' *(black)* was measured in the helical cardiac scan. ''AA high-pitch'' and the other levels *(white)* were measured in the high-pitch spiral scan of the aorta.
AA= ascending aorta; DA= descending aorta; AAo= abdominal aorta; RCIA and LCIA= right and left common femoral artery; RCFA and LCLA= right and left common femoral artery

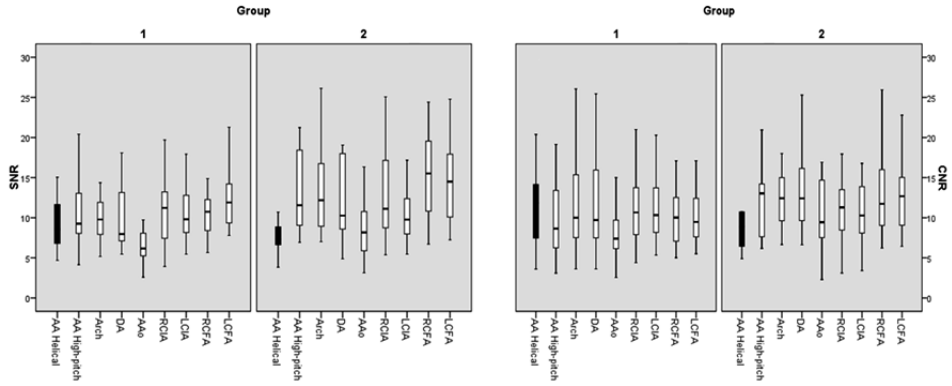

Figure 6.4 Box plots show SNR (left) and CNR (right) levels of each vascular segment
''AA helical'' *(black)* was measured in the helical cardiac scan. ''AA high-pitch'' and the other levels *(white)* were measured in the high-pitch spiral scan of the aorta.
AA= ascending aorta; DA= descending aorta; AAo= abdominal aorta; RCIA and LCIA= right and left common femoral artery; RCFA and LCLA= right and left common femoral artery

In helical scan images of the AA, sufficient enhancement levels (>200HU) were reached for both groups. Significantly higher attenuation values were observed for group 2 (mean attenuation group 1: 381±65HU; group 2: 442±68HU; p=0.004), whereas better SNR and CNR was observed for group 1 (SNR group 1 vs. group 2: 10±5 vs 8±2, p=0.045; CNR group 1 vs. group 2: 13±8, 10±5, p=0.152.
High-pitch spiral scan images achieved sufficient overall enhancement levels (>200HU) in both groups. A significantly higher mean attenuation was found at all levels of the aorta in group 1 (430±117HU) as compared to group 2 (389±102HU); p<0.001. Post hoc comparisons for each vascular segment revealed that the significant difference in attenuation existed at the levels of the RCIA, LCIA, RCFA and LCFA, with corresponding p-values 0.045, 0.016, 0.017 and 0.026. In none of the vascular segments the mean attenuation was <200HU, nor were individual attenuation levels of <200HU found at the level of the peripheral arteries (see **figure 6.3**)**.** Significantly higher SNR and CNR were found for group 2 (13±6 and 13±6) as compared to group 1 (11±6 and 11±6); p=0.017 and p=0.021, respectively (see **figure 6.4**)**.** Post hoc comparisons for each vascular segment revealed one mild significant difference between groups in the SNR at the level of the AAo, p=0.048.

IQ score *Helical*	Group 1 [n]	Group 2 [n]	P-value
1 2 3 4	0 0 12 17	0 1 13 4	0.03
IQ score *High-pitch*			
1 2 3 4	1 5 11 12	0 0 4 14	0.07
P-value	0.67	0.37	

Table 6.4 IQ scores of different anatomic levels for group 1 and group 2
IQ score: 1=non-diagnostic; 2=diagnostic; 3=good and 4=excellent

IQ scores of helical and high-pitch spiral acquisitions for both groups are listed in **table 6.4.** No significant differences were found between IQ scores of both acquisitions, with *p*-values of 0.67 for group 1 and 0.37 for group 2. IQ of each helical acquisition was diagnostic and IQ scores were significantly lower for group 2 compared to group 1 (p=0.03). No significant difference was found in IQ between both groups for the high-pitch spiral scans (p=0.07).

Renal function

The mean eGFR was 54±8ml/min/1.73m^2 and 55±8ml/min/1.73m^2 for group 1 and group 2 respectively. In 4 patients (9%) the eGFR was <45ml/min/1.73m^2. These values indicate the overall impaired renal function of this population. The mean eGFR ≥1-2 months after CTA was higher compared to the mean eGFR before CTA: 57±4ml/min/1.73m^2 and 57±6ml/min/1.73m^2 for group 1 and group 2 respectively. A constant eGFR was found in 32 patients, an increased eGFR in 13 patients and a decreased eGFR in two patients. In none of the cases CIN was detected after 1-2 months.

Prosthesis size	Number of patients	Measurements	
		Mean diameter [mm]	Area derived diameter [mm]
Edwards Sapien 3[A]			
23 mm	5	22	22
26 mm	15	25	25
29 mm	2	28	27
Edwards Sapien[A] XT			
20 mm	1	19	20
23 mm	1	22	22
Medtronic Engager[B]			
26 mm	1	23	24
Symetis Acuarte[B]			
23 mm	1	22	22

Table 6.5 Number of patients treated by different types of prosthesis as well as the annulus sizes measured by CT
[A] balloon-expandable prosthesis; [B] self-expandable prosthesis

TAVI procedure

In total, 26 patients were treated by TAVI and the survival rate after one month was 100%. Other patients underwent either open procedure or conservative treatment. In all patients the CT measurements were comparable to the size of the valve prosthesis implemented (**table 6.5**).

DISCUSSION

Vascular enhancement depends on three major factors – CM characteristics (e.g. flow rate), scanner related factors (e.g. tube voltage) and patient related factors (e.g. BMI). Especially use of lower kVp is advantageous in terms of reducing CM, as the same amount of iodine will lead to a higher enhancement at lower kVp[20], enabling substantial reduction in CM volume.[23-25] New scanner technologies facilitate lower kVp settings in a broader range of patients.[26] In addition, new reconstruction technologies such as iterative reconstruction (IR) reduce image noise and therefore improve image quality[27-30] at lower kVp settings as well. Using BMI adapted low volume CM injection protocols in combination with low kVp scan settings provided diagnostically sufficient image quality in pre-TAVI assessment. Compared to the 80 - 120ml CM mostly used in TAVI protocols[13], we were able to reduce CM volume to 40ml (=12gI) and 53ml (=16gI)

by using 70kVp and 80kVp settings, respectively. Further reduction of (10ml) would have been possible with use of bolus tracking, but a test bolus was chosen as additional information could be retrieved (e.g. cardiac output – beyond scope of this paper)[31] and which might be used for further adaptation of the injection protocol.[32]

Volume reduction up to 67% still lead to sufficient attenuation values at all anatomical levels in all patients. In addition, SNR and CNR levels were found to be sufficient for both groups according to Leber *et al*[21] who suggests CNR values >3 to be diagnostically acceptable.

Attenuation values, image noise and image quality ratios (SNR/CNR) are most affected by CM injection parameters, scan technique and patient body size[33]: Lowering IDR and TIL might compromise attenuation values and therefore image quality; Lowering radiation dose – by decreasing kVp or tube current settings – increases the amount of image noise; Increased body size decreases attenuation values due to increased circulating blood volume and simultaneously image noise increases due to absorbing tissue. These factors necessitate optimised injection and scan parameters in terms of image quality. However, individual patient characteristics and indication for CTA need to be taken into account. For TAVI candidates, optimal image quality – meaning low image noise and high enhancement – is required at the level of the aortic root for aortic annulus evaluation. For the peripheral access route, higher noise levels are acceptable. In this respect, IQ scores were defined according different criteria for each anatomic level in the current study. Comparisons between IQ at the level of the aortic root and the level of the peripheral arteries showed no significant differences in both groups. However, in one patient, image quality was found to be non-diagnostic at the level of the peripheral arteries due to the presence of prosthesis material. This could easily be picked up on the scout view and scan parameters can be adjusted accordingly (higher kVp settings). On the other hand metallic artefacts do not necessarily hinder full evaluation of the vessels.

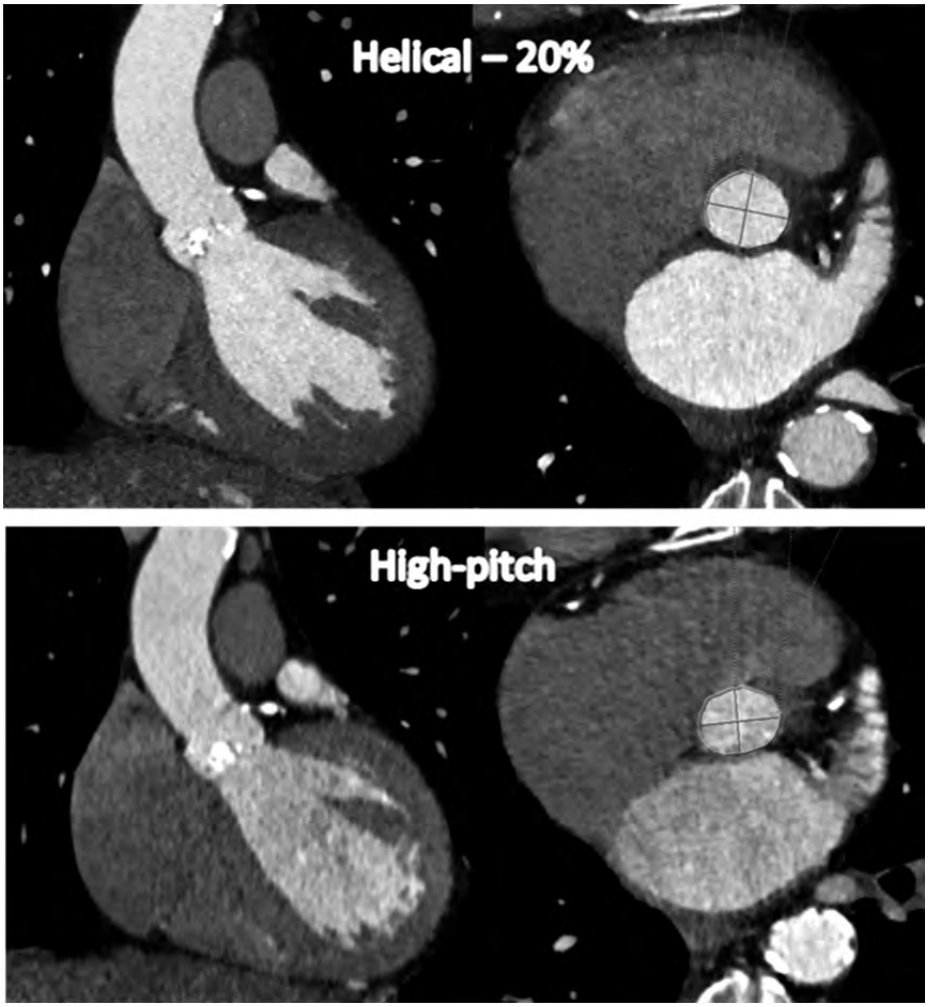

Figure 6.5 Images show the difference in the dimensions of the annulus and valve between reconstructions from different scan acquisitions
Reconstruction at the 20% phase of the cardiac cycle using retrospective ECG-gated helical acquisition *(upper)* and reconstruction using the non ECG-gated high-pitch acquisition *(bottom)*. The measurements for short and long diameter as well as perimeter were: 21mm, 25mm and 4.2cm², respectively for the helical acquisition and 19mm, 24mm and 3.8cm², respectively for the high-pitch acquisition

Optimising radiation dose is of less importance in this particular patient population, stochastic effects can be regarded as negligible in patients with a mean age of 75/76 years. But the most challenging and important part of protocol optimisation in a TAVI population with an inherent high number of impaired renal function, is to reduce the risk of CIN by means of the most efficient use of CM.[34, 35]
The use of reduced TIL in pre-TAVI assessment has been investigated by several other groups. For example, Dubourg *et al*[36] evaluated a combined CM injection protocol for

an ECG-gated helical scan followed by a non ECG-triggered high-pitch spiral scan. They used a dual energy acquisition with fast kVp switching (80-140kVp) for the second acquisition, and were able to reduce the second bolus CM volume by 50%. Total CM volume was reduced from 125ml to 95ml, which still results in a relatively high TIL (33gI using CM concentration of 350mgI/ml).

Wuest *et al*[37] were able to reduce CM volume to 40ml for CTA in TAVI candidates (14gI with 350mgI/ml). Patients with BMI <30 received a 100kVp scan protocol, with BMI >30 a 120kVp scan. Image quality (presence of motion artefacts, enhancement, image noise and CNR) for evaluation of aortic root complex was found to be diagnostic in 40 from 42 patients.

Azzalini *et al*[38] tested the feasibility of an ultralow CM volume injection (20ml = 7.4gI with 370mg/ml), in combination with a high-pitch scan mode in 8 patients. They found acceptable image quality using a 100 or 120kVp setting (automated tube voltage setting according patient body size). However, in these studies, only one scan – a high-pitch spiral acquisition – was performed for the evaluation of both aortic root and iliac dimensions, which compromises the dynamic assessment of the aortic valve and the annulus as retrospectively gated CTA – including a 20% phase reconstruction – is recommended.[17] **Figure 6.5** demonstrates the difference in dimensions of the annulus and valve between a 20% phase reconstruction from a retrospective ECG-gated helical acquisition and a reconstruction from a high-pitch acquisition – as the latter provides no 20% phase reconstruction. ECG-triggered high-pitch CTA is usually acquired during diastolic phase, and should therefore be used exclusively for aorto iliofemoral CTA.[2, 18, 36] Although differences between phases of reconstruction might be small, they will lead to different measurements for the diameter and could therefore lead to different prosthesis sizing.[17]

In none of the abovementioned studies a combined scan protocol including a retrospective ECG-gated acquisition was used. Either a high-pitch spiral scan acquisition was used in combination with low volume injections, at the expense of a dynamic study; or a combined scan acquisition was used at the expense of CM volume reduction. One could argue that the use of only one scan acquisition is most advantageous as this could reduce scan time and therefore radiation dose and CM volume. However, an ECG-triggered high-pitch scan acquisition is not desirable because of the reconstruction in the diastolic phase, as mentioned above. A complete retrospective ECG-gated acquisition is also not desirable as the scan time will greatly increase because of the decreased pitch factor compared to a high-pitch acquisition (0.23 vs. 3.0). As a result, radiation dose will increase and CM volume must also be adjusted according a prolonged injection time (see also **figure 6.6**).

The combined scan protocol as presented will therefore ensure best image quality at the level of the aortic root for dedicated pre-interventional analysis in combination with a full picture of the access options for TAVI, while keeping radiation dose and TIL as low as possible.

In the current study, the overall renal function was not impaired after 1-2 months from CTA. This is in line with the study of McDonald *et al*[39], which stated that intravenous iodinated CM may not be the causative agent in impaired renal function after CM administration.

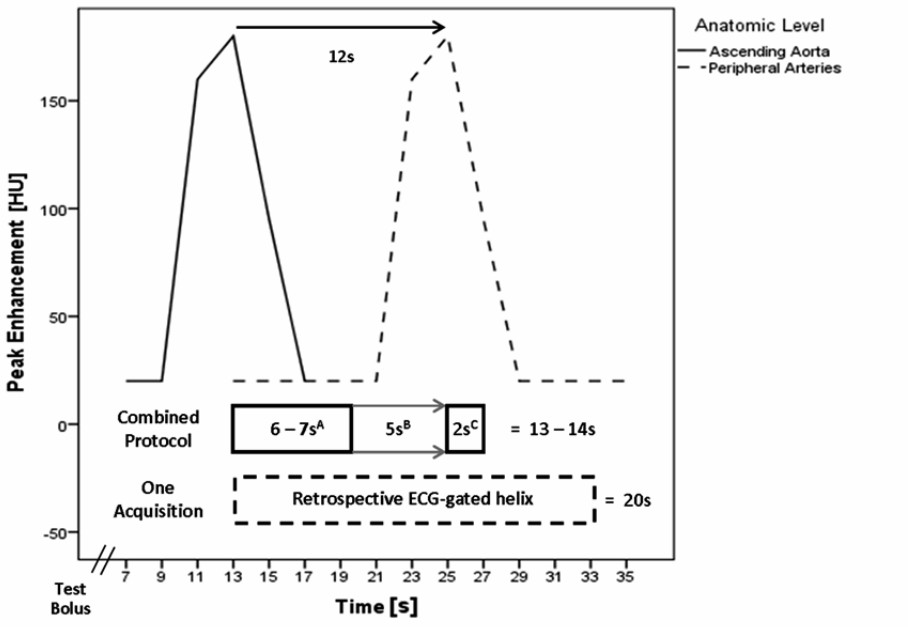

Figure 6.6 This schematic figure shows the time to peak at the level of the ascending aorta as well as at the level of the peripheral arteries
The time in between was 12s. Using the combined scan protocol, the fast second scan acquisition will again catch the bolus in the peripheral arteries. With only the retrospective ECG-gated acquisition scan time will be extended and the bolus will likely overtake the scan.
[A] retrospective ECG-gated helical acquisition of the heart; [B] gap between acquisitions; [C] high-pitch acquisition of the aorta from aortic arch to femoral arteries

Limitations

One limitation is that serum creatinine data from 48-72 hours after CTA could not be retrieved in the majority of patients and therefore acute kidney failure could not be detected. However, the eGFR after 1-2 months showed no relevant changes in renal function compared to the eGFR before CTA. In addition, ultra-low kVp scan protocols as well as the ultra-fast acquisition mode are not available on every type of scanner

and in the current situation the protocols are not applicable to every patient, due to technical limitations of the dedicated CT scanner used in this study: the maximum tube-current-time product for a high-pitch flash scan was 122mAs$_{eff}$ for 80kVp and only 93mAs$_{eff}$ for 70kVp. These low tube-current-time products present a problem because of resulting streak artefacts in the presence of prosthesis materials, or too high noise levels in obese patients.

CONCLUSION

Low kVp scan protocols allow for substantial reduction in CM volume as compared to common high volume injection protocols for pre-TAVI CT examinations. Sufficient image quality was maintained for the evaluation of the aortic root and peripheral access site despite a CM volume reduction of 34-67%. This may play an important role in terms of increased patient safety, as lower iodine load is regarded to lower the risk of CIN.

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CHAPTER 7

Individualised CT angiography protocols for the evaluation of the aorta: A feasibility study

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ABSTRACT

Purpose

Ionising radiation and iodinated contrast are potential drawbacks for repetitive follow-up CT angiography (CTA) in current practice. The aim of this study was to optimise radiation dose and contrast volume by using individualised CTA protocols.

Materials and methods

Eighty consecutive patients referred for CTA of the whole aorta were prospectively evaluated. Patients were divided into two groups: group 1: body mass index (BMI) <28kg/m^2 (n=50) and group 2: BMI≥28kg/m^2 (n=30). A control group was used and consisted of 50 consecutive patients who were retrospectively evaluated. CTA parameters on a 2nd generation dual-source scanner were: 128x0.6mm coll., pitch 0.9, rot.time 0.33s, 80/100/120kVp (group 1/group 2/control), 400mAs_{ref}; image reconstruction: 1mm/0.8mm slice thickness (kernel: B30f [control] and I30f, strength 3 [group 1/2]). The control group received 120ml of contrast (300mgI/ml) at 4.8ml/s; group 1 and group 2: 44ml and 53ml at 3.3ml/s and 4ml/s, respectively. Effective dose [mSv] was evaluated for each patient. Image quality was determined by qualitative image analysis at the level of the thoracic, abdominal and pelvic aorta: non-diagnostic/diagnostic/good/excellent and quantitative image analysis: attenuation values [HU] and contrast-to-noise ratio (CNR).

Results:

Mean effective radiation dose values for a CTA of the aorta were: 3.7±0.7mSv (group 1); 6.7±1.4mSv (group 2) and 8.7±1.9mSv (control) with p-values <0.001. Mean attenuation values and CNR levels were as follows (mean±SD): group 1: 334±66HU and 16±8; group 2: 277±56HU and 14±5; control: 305±77HU and 11±4.

Conclusion:

Iterative reconstruction algorithms resulted in 23-57% less radiation in combination with 55-63% less contrast volume when compared to standard CT protocols.

INTRODUCTION

Computed tomographic angiography (CTA) is widely used in current practice to detect aortic aneurysms, to evaluate aortic diameter over time and for follow-up after endovascular aneurysm repair (EVAR).[1,2] With technical improvements such as multi detector-row CT (MDCT) even more options exist to image anatomical structures, to visualise the aortic wall and lumen, calcifications and thrombus as well as metallic stent-grafts.[1,3-7] Furthermore, compared to other imaging methods, advantages of CTA include the fast image acquisition and easy post processing, the ability to obtain a three-dimensional (3D) reconstruction of the entire aorta, and the widespread availability of this method.[1] However, use of iodinated contrast and ionising radiation dose are considered potential drawbacks for CTA[1,8] – especially when lifelong follow-up imaging is recommended.[9-11] In order to minimise these risks, using as low as reasonably achievable radiation dose and subsequently lowering contrast volume[12] seem to be fair options. However, these protocol adaptations should not be at the expense of image quality. Therefore, the use of body weight adapted protocols[13,14] and new scanner options such as iterative reconstruction allow imaging at lower radiation dose without compromising image quality compared to routine dose filtered back projection (FBP).[15-17] For example, Lehti *et al*[18] could reduce radiation dose with 12% and iodine load with 48% using 80kVp compared to 120kVp. Chen *et al*[19] reduced radiation dose with 48% and iodine load with 60% in aortic CTA using 80kVp compared to 120kVp, while using iterative reconstruction. In both studies, however, scan protocols were not adapted according to patients' body size (mean body mass index (BMI) in both studies was approximately 27kg/m^2).

Taking all these factors into consideration, individualisation and optimisation of scan protocols as well as contrast administration according to patients' body size in CTA of the aorta, is warranted. Thus, the aim of this study was to evaluate the use of individualised aortic CTA protocols with interative reconstruction and to compare this with the use of standard CTA.

MATERIALS AND METHODS

Ethics and patient population

The study design was approved by the local ethical committee and the institutional review board. A waiver of written informed consent was obtained from the local ethical committee (METC, ref. 15-4-015).

Ninety-eight consecutive patients referred from the vascular surgery outpatient department underwent CTA for evaluation of different aortic diseases. The patients were divided into two groups and received an adapted scan and injection protocol based on

their BMI[20,21]: group 1 BMI <28kg/m^2 (n=50); group 2 BMI ≥28kg/m^2 (n=30). Patients with BMI ≥35kg/m^2 received a scan protocol without the use of lower kVp settings and were therefore excluded from the analysis (n=18). In total, 80 patients were prospectively included for this study. The control group was retrospectively included and consisted of 50 consecutive patients who received a standard scan and injection protocol with fixed parameters. Baseline characteristics such as age, gender and BMI of all groups are listed in **table 7.1**. Included patients received an aortic CTA for different clinical indications regarding the evaluation of the aorta as listed in **table 7.2**. In patients referred for a follow-up scan post TEVAR (thoracic endovascular aneurysm repair), EVAR or FEVAR (fenestrated endovascular aneurysm repair), the indication consisted of aortic diameter evaluation and stent-graft evaluation including its position and the detection of possible endoleakages.

Baseline characteristics	Control (n=50)	Group 1 (n=50)	Group 2 (n=30)	*P-value^*
Age [y]	68±11	67±12	64±12	*0.3*
Gender [male]	39 [78%]	30 [60%]	23 [77%]	*0.2*
Height [cm]	175±10	174±10	173±10	*0.2*
Weight [kg]	82±16	72±14	92±10	*0.2*
BMI* [kg/m^2]	26±4	24±3	30±3	*0.6*

Table 7.1 Baseline characteristics

*BMI = Body mass index

^The p-value is based on the difference between the control group and the intervention group (= group 1 and 2 together)

Clinical indication	Control (n=50)	Group 1 (n=50)	Group 2 (n=30)
CTA			
Aortic diameter (n=44)	15 [30%]	15 [30%]	14 [46%]
Pre intervention (n=13)	4 [8%]	7 [14%]	2 [7%]
Aneurysm			
1. mesenteric branches/arteries (n=5)	-	3 [6%]	2 [7%]
2. iliac/femoral arteries (n=5)	2 [4%]	2 [4%]	1 [3%]
Stenosis			
1. renal arteries (n=1)	-	1 [2%]	-
2. mesenteric branches/arteries (n=6)	3 [6%]	2 [4%]	1 [3%]
3. iliac/femoral arteries (n=2)	-	2 [4%]	-
CTA + additional scans			
Post intervention			
1. TEVAR (n=14)	6 [12%]	5[10%]	3 [10%]
2. EVAR (n=16)	9 [18%]	5 [10%]	2 [7%]
3. FEVAR (n=6)	4 [8%]	-	2 [7%]
Type B dissection (n=17)	6 [12%]	8 [16%]	3 [10%]
Bleeding (n=1)	1 [2%]	-	-

Table 7.2 Number of scans for different scan ranges and for different clinical indications among all groups

CTA scan and contrast injection protocols

All patients received a thoraco-abdominal-pelvic CTA. For the assessment of the aorta, scans were performed using a 2nd generation Dual-source CT scanner (Somatom Definition Flash, Siemens Medical Solutions, Forchheim, Germany) with a 128x0.6mm slice collimation; gantry rotation time of 0.33s and pitch value 0.9. The acquisition time for this scan range while using these parameters varies between 8-12 seconds depending on the scan range in the z-direction. Group 1 and group 2 received a scan protocol using a reference tube current of 400mAs$_{ref}$ (CareDose 4D^{TM}, Siemens Medical Solutions) and a tube voltage of 80kVp and 100kVp, respectively. The control group received a dual energy scan protocol using the following settings: a reference tube current of 136mAs$_{ref}$ and 116mAs$_{ref}$ (CareDose 4D^{TM}, Siemens Medical Solutions) for tube A and tube B, respectively and a tube voltage of 100kVp and 140kVp for tube A and tube B, respectively (dual energy composition of 0.5 [≈ 120kVp] for the mixed images).
Iodinated contrast (iopromide @ 300 mgI/ml ; Ultravist, Bayer Healthcare, Berlin, Germany) was pre-heated to body temperature (37˚C; 99˚F) and injected using a standard dual-head CT power injector (Stellant, Bayer Healthcare, Berlin, Germany). Patients from group 1 received a main contrast bolus of 44ml injected at 3.3ml/s and patients from group 2 received a main bolus of 53ml injected at 4ml/s. Patients from the control group received a main contrast bolus over 25s (120ml injected at 4.8ml/s).

All injections were followed by a saline flush of 40ml at the same flow rate. Scan delay was determined by bolus tracking technique. Contrast monitoring software (Certegra™ Informatics Solution, Bayer Healthcare, Berlin, Germany) was used to record the relevant contrast injection parameters (e.g. volume, flow rate, peak flow rate and peak pressure) for each patient.
Image reconstruction was performed using 1mm slice thickness with an increment of 0.8mm using a B30f kernel (FBP) for the control group and an I30f kernel (Sinogram Affirmed Iterative Reconstruction; [SAFIRE] strength 3) for group 1 and group 2. Scan parameters are summarised in **table 7.3.** All dose related parameters (e.g. effective tube current [mAs_{eff}], CTDIvol, dose-length product [DLP] and effective radiation dose) were recorded for each scan.

Group	Control	Group 1/ Group 2
Protocol	Aorta	Aorta
Mode	Spiral	Spiral
Collimation [mm]	0.6	0.6
Acquisition [mm]	128*0.6	128*0.6
Tube voltage [kVp]	100/140	80/100 (group 1/group 2)
Dose modulation	on	on
Tube current [mAs_{ref}]	136/116	400
Rot.Time [s]	0.33	0.33
Pitch	0.9	0.9
Delay [s]	Bolus tracking technique	Bolus tracking technique
Direction	Cranio-caudal	Cranio-caudal
Reconstruction 1		
Slice thickness [mm]	1.0	1.0
Increment [mm]	0.8	0.8
Kernel	B30f	I30f

Table 7.3 Scan protocol parameters

Quantitative analysis – radiation dose and image quality

Radiation dose monitoring software (Radimetrics™ Enterprise Platform, Bayer Healthcare, Berlin, Germany) was used to record the CTDIvol [mGy], DLP [mGy.cm] and the effective dose [mSv] from each CTA acquisition. The software calculates the effective dose using age- and sex-averages tissue weighting factors as described by the international commission on radiological protection (ICRP) in publication 103.[22]

All CTA images were analysed using multi-planar reconstruction with Syngo-Via™ software (Siemens Healtcare), f**igure 7.1**. Objective image quality was evaluated by measuring intravascular enhancement in Hounsfield Units [HU] by delineating circular regions of interest (ROI) in eight predefined vascular segments: ascending aorta (AA), aortic arch, descending aorta (DA), abdominal aorta (AAo), right and left common iliac artery (RCIA and LCIA) and right and left common femoral arteries (RCFA and LCFA). Image noise was defined as the standard deviation (SD) of the vessel attenuation. Contrast-to-noise ratio (CNR) was calculated by using adjacent muscle tissue enhancement and SD: CNR is the intraluminal attenuation minus intramuscular attenuation divided by the SD of the intramuscular attenuation. Attenuation values of 200-250HU are considered diagnostically sufficient for the evaluation of the aorta[23,24], e.g. general anatomy, calcifications, dissection, aneurysm and in selected cases the extension of disease into the aortic branches.

Quantitative image quality was independently analysed by two experienced readers who were trained for the analysis (MK, KD). Qualitative image analysis was determined by subjectively rating the contrast enhancement, image noise and the presence of artefacts at three anatomic levels (thoracic, abdominal and pelvic) using a 4-point Likert scale: 1=non-diagnostic image quality; 2=significantly reduced image quality, but still diagnostic for assessment; 3=good image quality and 4=excellent image quality.

Qualitative image quality was independently rated by two experienced observers (MK, MWH).

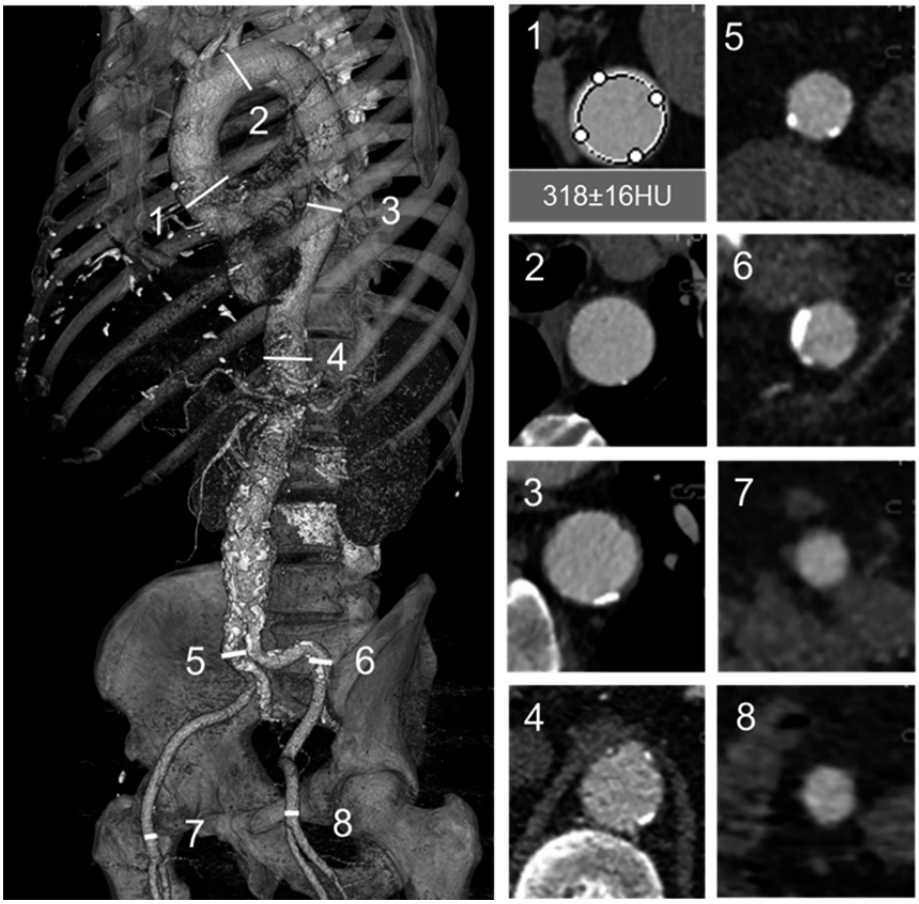

Figure 7.1 Images as reconstructed by Syngo-Via™ software
3D-reconstruction of the entire aorta (left) with given landmarks (right; 1-8). Landmarks were used for measurements of intravascular attenuation; (1) Ascending aorta; (2) Aortic arch; (3) Descending aorta; (4) Abdominal aorta; (5, 6) Right and left common iliac arteries as well as (7, 8) Right and left common femoral arteries

Statistical analysis

Continuous variables were expressed as mean±SD, categorical variables as absolute numbers [n] and percentages [%]. Continuous variables were compared using one-way ANOVA test and Tukey test was performed for post hoc comparisons between groups and between different anatomic levels. The chi-square test was used to measure differences between categorical variables. Intra-observer variability for the quantitative image analysis was evaluated by calculating intraclass correlation coefficients (ICC), using a two-way mixed model. ICC can be interpreted as follows: 0-0.2 indicates poor

agreement; 0.3-0.4 indicates fair agreement; 0.5-0.6 indicates moderate agreement; 0.7-0.8 indicates strong agreement and >0.8 indicates almost perfect agreement. Inter-rater agreement for the qualitative image analysis was evaluated by calculating Cohen's Kappa (K). Data analysis was performed using SPSS version 20.0 software (SPSS, Inc., Chicago, IL). All p-values are 2-sided, and a p-value lower than 0.05 was considered to be statistically significant.

RESULTS

Patients, radiation dose and contrast volume

No significant differences in baseline characteristics were found between the control group and the intervention group (group 1 + group 2; **table 7.1**). Mean CTDIvol [mGy], DLP [mGy.cm] and effective radiation dose [mSv] for each group are listed in **table 7.4.** Mean effective radiation dose for group 1 was reduced by 57% compared to the control group, with *p*-value <0.001. Mean effective radiation dose for group 2 was reduced by 23% compared to the control group, with *p*-value <0.001. Mean volume, flow rate and peak flow rate for the control group, group 1 and group 2 are listed in **table 7.4.**

Radiation dose parameters	Control (n=50)	Group 1 (n=50)	Group 2 (n=30)	*P-value*
Tube current CTA [mAs_{eff}]	*Tube A / Tube B* 122±26 / 101±23	204±24	205±18	
CTDIvol CTA [mGy]	24±5	17±5	19±3	
DLP CTA [mGy.cm]	650±113	286±57	570±88	
Effective dose CTA [mSv]	8.7±1.9	3.7±0.7	6.7±1.4	*<.001**
CM injection parameters				
Applied volume [ml]	119±2	44±0	53±0	
Applied flow rate [ml/s]	4.8±0.1	3.2±0.0	3.9±0.1	
Peak flow rate [ml/s]	5.1±0.1	3.6±0.2	4.2±0.0	
Peak pressure [psi]	89±11	62±12	72±16	

Table 7.4 Radiation dose and injection parameters (mean±SD), recorded from each scan
*Significant difference was found between all groups after post hoc comparisons

Image quality

Mean attenuation values (HU±SD) for the control group, group 1 and group 2 were diagnostic (>200HU): as shown in **figure 7.2.** In the control group, non-diagnostic enhancement levels were found in two patients; in one of them the overall enhancement level was <200HU. In the other patient, a large infra-renal aneurysm caused non-diagnostic enhancement levels in the iliac and femoral arteries. No non-diagnostic enhancement levels were found in patients of group 1 and 2. Corresponding mean CNR values are shown in **figure 7.2.** Lowest CNR values were found at level of the AAo as well as at the level of the RCIA and LCIA due to the higher amount of image noise in the abdomen caused by surrounding tissues. Qualitative image quality is listed in **table 7.5.** In groups 1 and 2, all scans were graded 'diagnostic', 'good' or 'excellent' at each anatomic level. In two scans of the control group enhancement levels were <200HU, however, the indication for CTA in the scan with overall enhancement levels <200HU was 'evaluation of aortic diameter' and this could be properly depicted although the low enhancement levels. In the other patient, the indication for CTA was 'aortic anatomy pre intervention' and the enhancement level was not diagnostic for assessment at the level of the peripheral arteries. Therefore, the scan was graded 'non-diagnostic' at this level (**table 7.5**).

Reproducibility of quantitative image quality measurements proved to be excellent: as the intraclass correlation coefficient was 0.986 and this indicates almost perfect agreement.

Inter-rater agreement of the qualitative image quality analysis was strong at each anatomic level: thoracic = 0.81; abdominal = 0.79 and pelvic = 0.78, respectively.

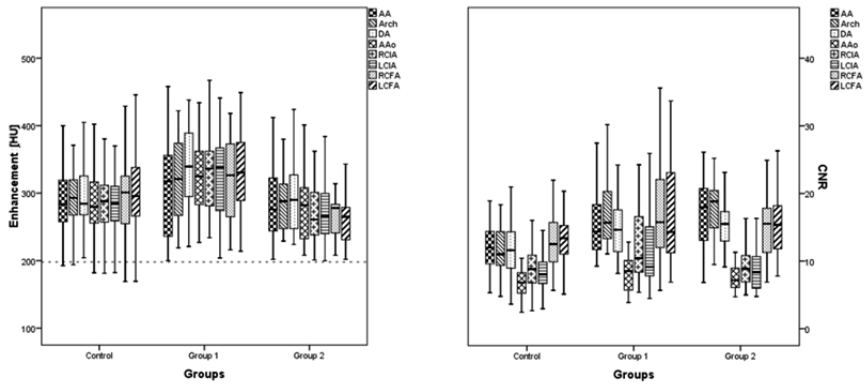

Figure 7.2 Box plots show the intravascular enhancement (left) as well as the CNR values (right) at different anatomic levels for each group

Qualitative image quality (Likert score)	Control (n=50)	Group 1 (n=50)	Group 2 (n=30)	*P-value*
Thoracic aorta				*0.77*
1	-	-	-	
2	1 [2%]	-	-	
3	4 [8%]	3 [6%]	2 [7%]	
4	45 [90%]	47 [94%]	28 [93%]	
Abdominal aorta				*0.48*
1	-	-	-	
2	1 [2%]	-	-	
3	12 [24%]	7 [14%]	5 [17%]	
4	37 [74%]	43 [86%]	25 [83%]	
Pelvic aorta				*0.45*
1	1 [2%]	-	-	
2	1 [2%]	1 [2%]	1 [3%]	
3	8 [16%]	11 [22%]	4 [14%]	
4	40 [80%]	38 [76%]	25 [83%]	

Table 7.5 Qualitative image qualities at different anatomic levels for the control group, group 1 and group 2 1=non-diagnostic; 2=diagnostic; 3=good and 4=excellent

DISCUSSION

The use of BMI adapted aortic contrast-enhanced protocols (thoraco-abdominal-pelvic) resulted in a radiation dose reduction of approximately 57% for patients with a BMI<28kg/m^2 and approximately 23% for patients with a BMI ≥28kg/m^2 and <35kg/m^2 as well as for a contrast volume reduction of 63% and 55%, respectively. These reductions were achieved by using lower tube voltages in combination with iterative reconstruction compared to the 120kVp protocol in combination with FBP which is used in our institution (**figure 7.3**). These results reveal that an injection time of 13.3s (groups 1 and 2) already turned out to be robust in providing diagnostic enhancement at each aortic level for an acquisition time of 8 – 12s.

Furthermore, the results also show that diagnostic scans were obtained using BMI adapted protocols; all scans being graded as 'diagnostic', 'good' or 'excellent'.

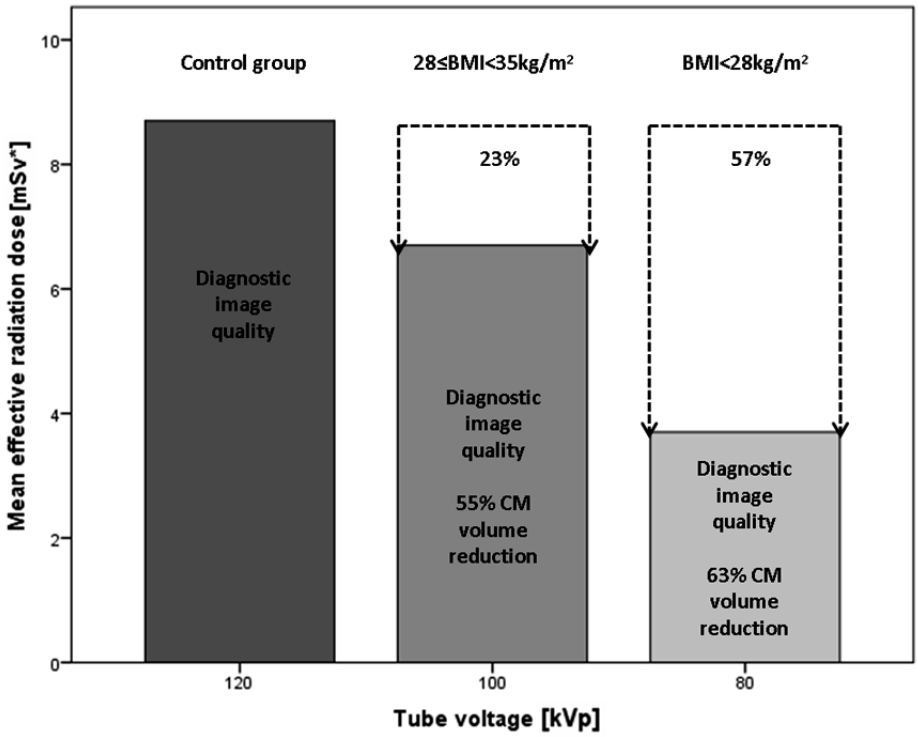

Figure 7.3 Bar graphs and arrows show the achievable reduction of radiation dose exposure and CM volume for a thoraco-abdominal-pelvic CTA for patients with a BMI<35kg/m^2
*Radiation dose [mSv] was calculated by Radimetrics^{TM} Enterprise Platform (Bayer Healthcare, Berlin, Germany)

Objective image quality was slightly better for group 1 and group 2 compared to the control group. Previous research already found that the application of iterative reconstruction resulted in better quantitative image quality compared to FBP.[25,26] This means that reduced tube voltage potentially improves CNR because contrast enhancement increases at lower kVp settings and image noise decreases with the use of iterative reconstruction.[27] However, in the present study, the injection protocol was adapted to the lower kVp settings and differences in quantitative image quality were therefore limited. Moreover, the scan protocol used for the control group was dual energy, which makes the comparison between iterative reconstruction and FBP unreliable. This comparison, however, was not the primary goal and more important is the fact that diagnostic scans were provided while radiation dose exposure and contrast volume could be reduced in comparison to the standardly used CTA protocol.
With respect to the image quality for different clinical indications and the impact on radiation dose exposure, there are two important influencing factors. First, CTA only will not provide enough image quality for each indication; a non-enhanced CT followed

by CTA is – for example – particularly recommended for suspected bleeding or dissection[1,28] and delayed-phase CT in addition to CTA is recommended for suspected bleeding or after EVAR procedure in order to detect endoleakage.[1,7] These additional scans will provide a significant increase in radiation exposure for these patients but are certainly desirable for diagnosis and follow-up. Second, there are also technical parameters influencing the diagnostic image quality for a specific indication. Image noise and intravascular enhancement are important parameters indicating image quality. High image noise levels and low intravascular enhancement might therefore lead to non-diagnostic scans. For CTA of the aorta there are several different indications. For example: in case of suspected stenosis (renal/mesenteric arteries) optimal image quality is required for the adequate assessment of these smaller vessels, meaning a combination of high intravascular enhancement and low image noise should be pursued. For evaluation of the aortic diameter only, higher image noise levels are acceptable. In this study, none of the CTA's using reduced radiation dose and contrast volume were rated as non-diagnostic, indicating that the current radiation dose and contrast volume reduction is a reliable option for a broad range of indications and even more reduction might be possible for measuring the aortic diameter only.

The current study shows that cumulative radiation dose exposure over the first year – including 4 recommended time points[2,7] – will be approximately 35mSv (control group; 4*8.7mSv). As CTA protocols would be adapted to patient body size, the expected cumulative value is 15.8mSv for patients with a BMI<28kg/m^2 and 27mSv for patients with a BMI>28kg/m^2. In addition, contrast volume would also be reduced from 480ml for the control group to 176ml and 212ml for group 1 and 2, respectively in the first year.
The current study provides an overview of reducing radiation dose and contrast volume for the individual patient, giving insight into decreasing potential drawbacks for CTA imaging. The range of patients who will benefit from reduced radiation dose and contrast volume is only expected to increase in the future due to ongoing advancements in detector technology of newer scanners – making the use of lower kVp settings, including 70kVp, possible in patients of different sizes.[29,30]

Limitations

This study has several limitations: it is a single center study performed on limited number of patients, especially for group 2. A larger study population would improve the impact of the results. Furthermore, the control group was retrospectively included and it would have been of additive value for the quality of the methods if the control group was also prospectively included. In addition, adaptation of additional non-enhanced scan acquisitions and delayed-phase scan acquisitions would be desirable as well, as

they significantly increase the overall radiation dose. However, this was not the goal of present study.

CONCLUSION

Individualised CTA protocols based on the BMI of the patient are favourable for CTA of the whole aorta in routine clinical practice. Iterative reconstruction algorithms resulted in 23-57% less radiation in combination with 55-63% less contrast volume when compared to standard CT protocols.

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CHAPTER 8
General Discussion

This thesis showed that CM injection protocols and scanning parameters can be optimised by making use of individualised medicine in routine CTA examinations; CM volume and radiation dose being used more efficiently while maintaining diagnostic image quality.

In order to optimise CTA protocols for the individual patient, broad knowledge about injection and scanning parameters is required. Therefore, this thesis starts with exploring the basics of CM characteristics and the influence of different CM injection parameters and scanning parameters on image quality in phantom studies. After that, the clinical application was investigated for different clinical CTA indications.

Based on **Chapter 2**, we can conclude that the amount iodine per milliliter within CM is directly correlated to the viscosity of CM, although this relationship was not linear. The highest concentration CM (400mgI/ml) was associated with the highest viscosity. Increasing temperature of CM (to body temperature [37˚C]) substantially decreased the viscosity of CM, however, the viscosity of the highest 400mgI/ml CM at body temperature was still significantly higher compared to the viscosity of the lower concentrations (240mgI/ml and 300mgI/ml) at room temperature (20˚C). Consequently, lowest injection pressures were found for CM of 240mgI/ml and 300mgI/ml at 37˚C. These findings implicate and stress the positive effect of preheating CM in order to reduce viscosity and therefore, to reduce injection pressure. Furthermore, due to the decreased injection pressure higher flow rates might be facilitated without increasing the risk of complications whilst using lower concentrations of CM. In that respect, in an ongoing research project we investigate patient comfort during injection of higher flow rates in a large patient population.

In **Chapter 3**, the influence of different CM concentrations on radiation dose reduction was investigated. From literature, it is already known that automated kVp-selection is strongly effective in terms of radiation dose reduction.[1-4] Our investigation showed that radiation dose reduction was independent of the CM concentration – as long as the IDR and TIL were kept identical.

Switching to lower tube voltage settings using automated kVp-selection is only feasible over the whole scan length. Tube current modulation, however, gives the opportunity to reduce tube-current-time product per slice.[5-7] Both dose modulation techniques highly depend on the body size of the patient and the anatomical area(s) within the scan range. As this was a phantom study, no patient related factors such as BMI, weight or thoracic/abdominal diameter could be included. Even though dose reduction is independent of the CM concentration used, the performance of both dose modulation techniques should be investigated in a broad range of patients – and, preferably on a scanner with possibilities of a broader range of tube voltage settings.

A logical next step was to investigate how to optimise attenuation values and injection parameters when using different tube voltage settings in a patient experiment.

Chapter 4 first includes a phantom study, which was performed in order to explain how to adapt IDR and TIL while using lower tube voltages. Then, a part of this investi-

gation was performed in 60 patients referred for CCTA. We could conclude that TIL and therefore CM volume could be reduced up to 56% at 70kVp – whilst maintaining diagnostically sufficient attenuation values within the target vessels. Initial results in patients confirmed this finding at 100kVp using 12% reduction of CM volume in CCTA compared to the CM volume used at 120kVp. These results may promote understanding of how to apply lower tube voltages on an individual basis, how to directly link contrast parameters such as IDR and TIL to tube voltage, and how to subsequently optimise contrast and dose settings.
Empirically dose reduction of CM has been reported by other groups as well[8-10] – they used 100kVp with 10-20% CM reduction in patients with a BMI<25kg/m^2, or they used 80kVp with 30% CM reduction in patients with a mean weight of 58-60kg. However, no systematic approach to reduce CM volume at different kVp settings was used in these studies.
Lell *et al*[11] performed a systematic approach for the thoraco-abdominal aorta. They concluded that adjusting IDR to a specific kVp setting indeed provided comparable arterial enhancement levels. Therefore, our systematic approach might serve as a profound basis for the imaging of other vascular territories.

The idea of applying CM injection parameters according to patients' body size and the specific clinical indication is presented in **Chapter 5.** In this study, patients suspected of pulmonary embolism (PE) and therefore referred for CTPA received CM injections individually adapted according to their body weight and scan duration. For this emergency indication, the scan protocol should be expected to deliver robust and reliable results twenty four hours a day, seven days a week. This study shows a greater consistency of vascular enhancement – indicating a more reliable protocol – using individualised injections compared to injections with fixed parameters. Even under emergency conditions it was feasible to adapt the most important injection parameters (e.g. flow rate, IDR) to the individual patient.
Some studies on body weight adapted CM protocols for CTPA in selective, low weight patient groups have been published: Holmquist *et al*[12] used an 80kV protocol with TIL of around 13g in a low weight patient group and Kristiansson *et al*[13] reduced the TIL in a similar patient group even further to 9.6g. However, 8-12% of the examinations were regarded as suboptimal. A CTPA with arterial attenuation below 180HU may be considered to be of non-diagnostic quality to reliably detect subsegmental emboli as mean HU values for acute and chronic embolism are around 33HU and 87HU, respectively.[14] In our study, all patients met this crucial cut-off value of 180HU.
Using the current approach; patient related factors (e.g. body weight) and the clinical indication (e.g. specific scan acquisition and duration) have been already taken into account. However, since tube voltage is an important influencing factor regarding contrast enhancement as well, future research should focus more on a complete individual adaptation of CM injections using a similar approach with the addition of the

factor tube voltage – for example by using the automated-kVp selection tool in combination with the reduction percentages for injection parameters as elaborated in **Chapter 4**.

The next step was to combine individualised injection protocols with individualised scan protocols in a broader range of CTA examinations; the use of iodinated CM and ionising radiation dose being an intrinsic matter of concern in general CTA.[15]

Chapter 6 mainly focused on the most efficient use of CM as TAVI candidates are frequently suffering from impaired renal function and are considered to be at increased risk of CIN.[16,17] Especially use of lower tube voltages enables substantial reduction of CM volume[9,18,19], as the same amount of iodine will lead to a higher enhancement at lower tube voltage.[20] However, image noise increases at lower kVp settings, mainly due to higher absorption of low-energy photons by the patient.[21] Nowadays, new reconstruction technologies such as IR improve image quality in comparison to routinely used FBP, as IR reduces image noise.[22-25] Therefore, IR was used in order to maintain diagnostic image quality whilst using reduced radiation dose. We could conclude that despite a CM volume reduction up to 67% – compared to the generally used volumes for pre-TAVI CT examinations[26] – diagnostic image quality could be provided by performing 80kVp and 70kVp scans while using IR. In addition, the overall renal function was not impaired after 1-2 months post CTA. However, the prevalence of CIN could not be evaluated as data from 48-72 hours after CTA was inconsistent in the majority of patients. One method could be to set up a large cohort study referred for pre-TAVI CT examination and to structural test renal function right before CTA and after 24-72 hours from CTA in order to quantify the incidence of CIN in this patient population.

The potential drawbacks of CTA will be even more pronounced when frequent imaging over time is recommended due to the related high cumulative radiation dose and repetitive administration of iodinated CM – especially in patients for follow-up of EVAR.[27,28] Based on **Chapter 7**, we could conclude that 23–57% radiation dose in combination with 55–63% CM volume might be saved compared to standard CTA aorta protocols. These reductions were achieved by using lower tube voltages [kVp] in combination with IR. A few studies investigated the influence of using IR on CTA of the aorta: For example, Lehti *et al*[29] reduced radiation dose with 12% and iodine load with 48% using 80kVp compared to 120kVp. Chen *et al*[30] reduced radiation dose with 48% and iodine load with 60% in aortic CTA using 80kVp compared to 120kVp, while using IR. In both studies, however, scan protocols were not adapted according to patients' body size (mean BMI in both studies was approximately 27kg/m^2).

As non-enhanced CT scans followed by CTA are particularly recommended for suspected bleeding or dissection[15,31] and delayed-phase CT scans in addition to CTA are recommended for suspected bleeding or after EVAR procedure in order to detect endoleakage[15,27], adaptation of these additional acquisitions in the future would be desirable as well, as they significantly increase the overall radiation dose.

Future perspectives

Currently, the demanding need for imaging is still growing. Therefore, the range of patients who will benefit from individually adapted use of radiation dose and CM volume is only expected to increase in the future. In addition, due to the advancements in detector technology of newest scanners – and especially in adaptation of tube-current-time product – the use of lower tube voltage settings, including 70kVp, might be possible in patients from all different sizes, as dose settings (e.g. CTDIvolume, [mGy]) may remain equal at each kVp setting.[32-34]

Furthermore, the content of this thesis mainly focused on the individual optimisation of different CM injection and scan protocols in order to maintain diagnostic image quality for the assessment of CTA images. The basis of achieving diagnostic image quality while using individualised protocols – and in particular diagnostic arterial enhancement – was already investigated and confirmed by the different manuscripts within this thesis.[35] However, when combining individualised injection and scan parameters, knowledge should be acquired regarding cut-off values for clinically used image quality parameters such as SNR and CNR. In order to understand these ratios and make it possible to actually provide specific cut-off values, the amount of image noise achieved by particular dose related parameters should be investigated in the future. Most important is to understand the underlying principles of the relation between image noise and diagnostic image quality for the specific indication and vascular structure, as well as the relation between dose related parameters used by the scanner (e.g. tube voltage, tube-current-time product) and image noise. **Figure 8.1** shows an example of a stepwise approach regarding the requirement of image quality for different CTA indications. The question is, how much image noise we may accept for the assessment of each vascular structure in combination with the clinical indication, and, which tube voltage and tube-current-time product settings do we need to use in order to achieve these image noise values. In addition, what is the exact influence of different reconstruction methods such as FBP and IR. With respect to these parameters, we want to investigate this at different types of scanners as well as in patients from different sizes.

1 Clinical indication	2 Required signal-to-noise ratio [SNR]	3 Vessel diameter	4 Relative required radiation dose	5 Dose settings
Cardiac				
-Coronary arteries	High	Small	Normal	
-Triple rule out	High	Large and small	Normal	
PE	Moderate	Large and small	Normal	
TAVI				Type of scanner
-Aortic root (ECG-triggered)	High	Large	Moderate	
-Full aorta (high-pitch)	Low	Large and small	Low	
Aorta				
-Aortic aneurysm	Moderate	Large	Low	
-Type A dissection	High	Large	Moderate	
-Type B dissection	High	Large	Moderate	Patient
-Pre EVAR	Moderate	Large and small	Moderate	
-Post EVAR (endoleakage)	High	Large and small	Normal	
-Bleeding	High	Large and small	Normal	
-Stenosis (mesenteric/visceral)	High	Small	Normal	

Figure 8.1 Example of a stepwise approach

CONCLUSION

In conclusion, individualised scan and injection protocols allow for a more efficient use of radiation dose and CM volume whilst diagnostic image quality could be maintained. Newest CT technologies allow even faster scanning as well as use of low tube voltages (e.g. 80 and 70kVp) in a broader range of patients. Further research should focus on how to efficiently apply radiation dose and CM volume in routine CTA in the future using these newest CT technologies.

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CHAPTER 9

Summary

Valorisation

Dankwoord

Curriculum vitae

List of publications

9.1
Summary

This thesis addressed several topics on individual optimisation of contrast media (CM) volume and radiation dose for different CT angiography (CTA) examinations. The overall focus of this research was to maintain diagnostic image quality in CTA while using iodinated CM and radiation dose in a more efficient way for the individual patient.

In **Chapter 2** the relationship between CM concentration and viscosity was described. The results show that the viscosity of CM lower with lower concentrations of iodine (240mgI/ml and 300mgI/ml) was significantly lower compared to CM with higher concentrations of iodine (370mgI/ml and 400mgI/ml). Furthermore, pre-heating CM to body temperature drastically decreased the viscosity of CM. In addition, the influence of different viscosity levels was investigated in circulation phantom, where CM was injection at different temperatures (20 – 37˚C). From these experiments, we could conclude that the injection pressure significantly decreased while using lower concentrated CM and, moreover, when injecting these concentrations at body temperature. Therefore, standardised pre-heating should be a prerequisite for clinical CM administration.

In **Chapter 3** the potential for automated kVp-selection to reduce the radiation dose during CTA using different concentrated CM – normalised to an identical iodine delivery rate (IDR; [gI/s]) – was explored using a circulation phantom. The results showed that automated tube current modulation can result in radiation dose reduction up to 53% and automated tube voltage selection up to 77%, if human subjects approximate the dimensions and therefore the attenuation values of the phantom used in the experiment. Furthermore, Dose reduction was – as expected – independent of the CM concentration applied at normalised IDR.

In **Chapter 4** the influence of scan parameters – especially tube voltage [kVp] settings – on intravascular enhancement in coronary CTA (CCTA) was investigated. A circulation phantom was used to systematically investigate how IDR and CM volume could be adapted to a particular kVp setting in order to remain optimal enhancement levels in the coronary arteries. These primary results were then also tested in sixty patients referred for CCTA. In a circulation phantom, lower kVp settings allowed a substantial reduction in CM volume - up to 56% at 70kVp - whilst maintaining diagnostically sufficient attenuation within the target vessels. Furthermore, initial results in patients confirmed this finding at 100kVp using 12% reduction of CM volume in CCTA.

In **Chapter 5** the effect on image quality when using body weight adapted injections was studied in patients referred for CT pulmonary angiography (CTPA). The use of individualised CM protocols provided diagnostic and robust enhancement in emergency CTPA, as well as a substantial CM volume reduction in lower weight patients compared to a fixed CM protocol. Moreover, greater consistency of vascular enhancement

values – indicating a more reliable protocol – was observed throughout the patients who received body weight adapted injections, whereas the scans for patients who received fixed injections showed a steady decline in attenuation with increasing body weight.

In **Chapter 6** the role of individual adaptation of both injection and scan protocols based on patient's body mass index (BMI) was elaborated in patients referred for pre-TAVI CT examination. As these patients frequently suffer from an impaired renal function, the possibility of reducing CM volume while using lower kVp settings was investigated. The use of low kVp (80kVp and 70kVp) scan protocols allowed for substantial reduction in CM volume as compared to common high volume injection protocols for pre-TAVI CT examinations. Sufficient image quality was maintained for the evaluation of the aortic root and peripheral access site despite a CM volume reduction of 34-67%.

In **Chapter 7** the possibility of reducing radiation dose exposure and CM volume was studied in patients referred for the evaluation of the aorta, as aortic CTA is associated with frequent follow-up over time, which implies high cumulative radiation dose and iodinated CM volume for these patients. It turned out that individualised CTA protocols based on the BMI of the patient are favourable for CTA of the whole aorta in routine clinical practice. Iterative reconstruction algorithms resulted in 23-57% less radiation in combination with 55-63% less contrast volume when compared to standard CT protocols.

9.2
Valorisation

INTRODUCTION

Computed tomographic angiography (CTA) is an imaging method which is widely used as a diagnostic tool for the visualisation and evaluation of various vascular structures. CTA has several advantages over other image modalities, for example because of its widespread availability and the short time required for image acquisition and processing. Furthermore, technology of CT imaging has undergone many changes in the past two decades; especially the advent of multidetector-row CT with high spatial and temporal resolution, wider detector coverage, increased rotation speed and iterative reconstruction improved image quality, resulting in improved visualisation of these various vascular structures. However, there are also potential drawbacks for CTA, including the administration of iodinated contrast media (CM) – which may cause allergic reactions or contrast induced nephropathy (CIN) – as well as the use of ionising radiation dose due to the risk of stochastic effects.
Consequently, it is important to select CTA protocols where patients will benefit from individualised application of iodinated CM and radiation dose in order to use iodinated CM and radiation dose in a more efficient way and to reduce the general drawbacks for CTA.

RELEVANCE OF SCIENTIFIC RESULTS

This thesis addressed several topics on individual optimisation of CM volume and radiation dose for different CTA examinations. For a long time the injection and scan protocols were standardised, in order to ensure diagnostic image quality in all patients, on the basis of the vascular structure that needed to be scanned. This resulted in so-called ''one size fits all'' protocols, which means that every patient received the exact same amount of radiation dose and iodine. One can imagine that not every patient needs this amount of iodine and radiation dose, whereas other patients may need some more in order to maintain diagnostic image quality. It has already been described in literature that body weight and body mass index (BMI) significantly correlate with image quality; higher body weight and BMI will decrease intravascular enhancement and increase image noise, resulting in deterioration of image quality.
The results from this thesis showed that CM volume and radiation dose in CTA could be significantly reduced by individual adaptation of protocols with respect to body size of the patient and clinical indication for the scan. Therefore, we would advise to use individualised CTA protocols in current routine practice; minimising the possible adverse effects of iodine and radiation dose in patients.

TARGET GROUPS

The results of this thesis are relevant for radiologists, and in particular, vascular radiologists as well as for the treating physicians in this case such as cardiologists, vascular surgeons and internists. For the treating physicians it could be important for decision making in the referral for CTA. Furthermore, patients who are referred for CTA and especially the relatively young patients and patients suffering from an impaired renal function can benefit from the individualised protocols.

INNOVATION AND REALISATION

This thesis first shows a standardised way of applying lower radiation dose on an individual basis, directly linking contrast parameters to radiation dose, and subsequently optimising contrast and dose settings. Eventually, there will be a lot of costs that can be saved because of the fact that the amount of CM can be drastically reduced in many cases.
It must be very clear that ''one size fits all'' protocols are outdated now. Obtaining diagnostic attenuation values using reduced CM volumes and radiation dose will play an important role in the future – especially due to the ongoing advancements in detector technologies. Newest CT technologies allow for even faster scanning as well as for the use of low tube voltages (e.g. 80 and 70kVp) in a broader range of patients. Further research should focus on how to efficiently apply radiation dose and CM volume in all different routine CTA protocols using these newest CT technologies.

9.3
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9.4
Curriculum vitae

Madeleine Kok was born the 30th of April 1988 in Amsterdam, the Netherlands. She grew up in Beek and finished her secondary school in Geleen. After secondary school, she started her medical training at Maastricht University in 2006. In her final year as a student she became involved with Dr. Das and Prof. dr. Wildberger's research regarding the use of contrast media in computed tomographic angiography. After obtaining her medical degree in October 2013 she became a PhD fellow under supervision of Prof. dr. Wildberger, Dr. Das and Dr. Kietselaer, focusing on the optimisation of contrast media and radiation dose for the individual patient. She presented her work at several national and international conferences. The most important results are described in this thesis. While completing her PhD, she assisted and trained new students who became members of the research team. From February 2016 Madeleine is working as a resident in Radiology at the University Medical Centre in Utrecht under supervision of Dr. R.A.J. Nievelstein.

9.5

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