Computed tomography of the abdomen

COMPUTED TOMOGRAPHY OF THE ABDOMEN:

From one size fits all to custom-made

Bibi Martens

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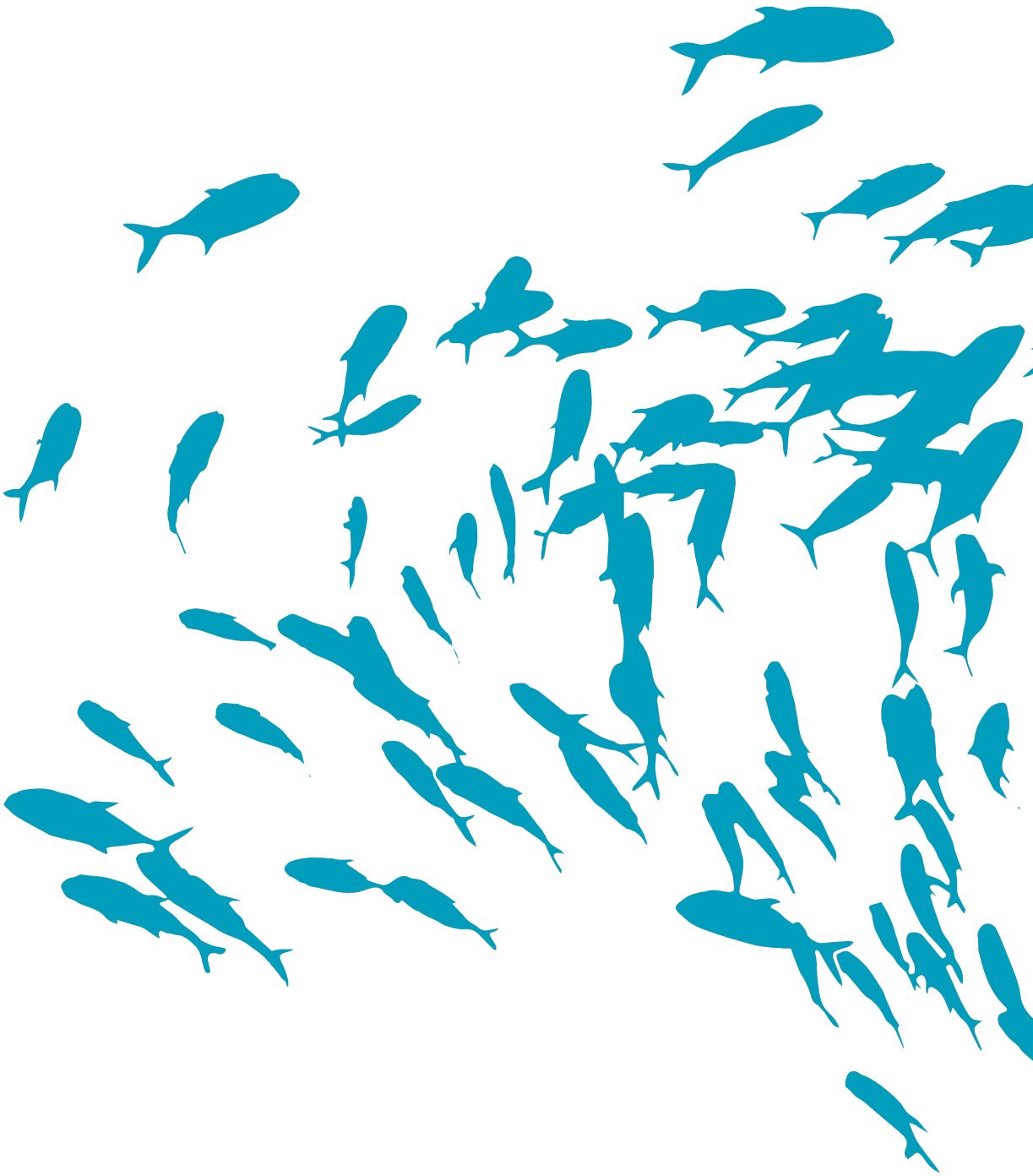
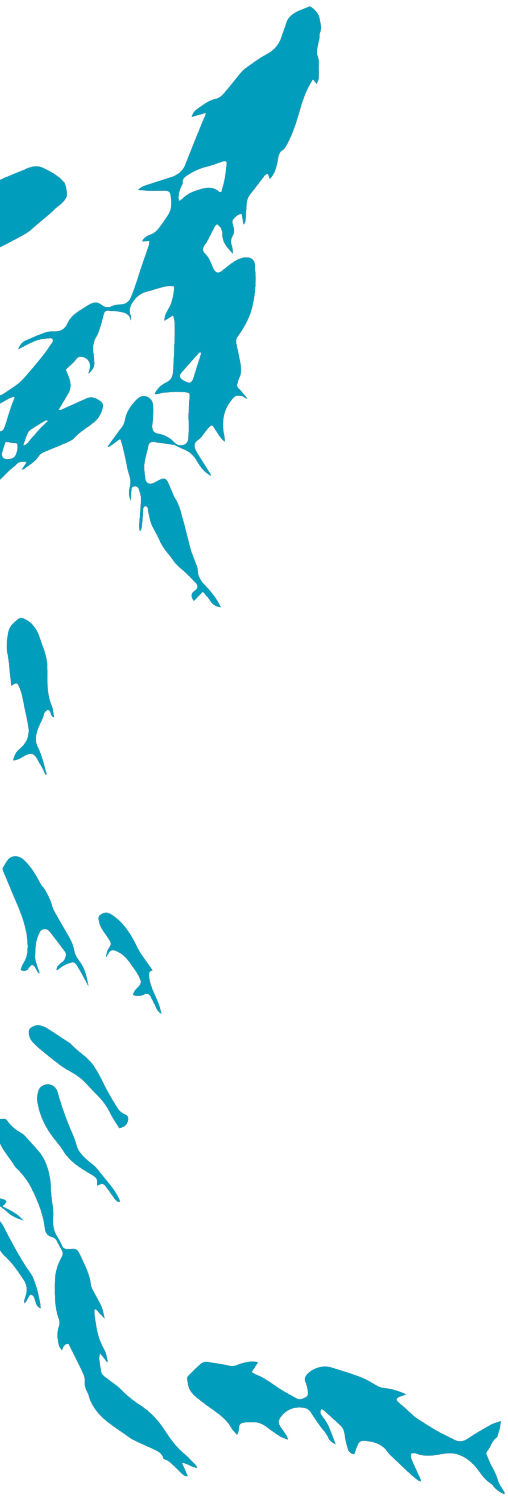




CHAPTER 1

General introduction

Millions of Computed Tomography (CT) scans are performed worldwide each year, with a large variety of scan and contrast media (CM) protocols (1). Non-invasive CT is the first-choice imaging modality for various clinical questions, such as oncological (follow-up) and infectious or vascular evaluation. Over the years faster scanners with high spatial and temporal resolutions have made CT a workhorse of daily clinical practice (2).

CT is associated with ionizing radiation, which in case of high exposure may lead to an increase in the lifetime attributable cancer risk (3, 4). This is the main reason for universal application of the "as low as reasonably achievable" (ALARA) principle (5). A large number of studies have focused on decreasing radiation dose (6-13). Radiation dose can be reduced by decreasing tube current and/or tube voltage. Initially, only tube current reduction was available, but presently tube current can be freely modulated. In addition, the development of more powerful tubes has enabled lower tube voltage, albeit limited to only few settings.

In the past, 'one size fits all' protocols were used for both radiation and CM injection. In other words, all patients were scanned with the same tube current and tube voltage, regardless of clinical question or body composition. At present, both parameters are determined before scanning, based on the scout view, and further adjusted during the examination to optimize radiation dose for each individual patient and body part. Automated tube current modulation (ATCM) and automated tube voltage selection (ATVS) techniques, currently present on the majority of newer scanners, have made it easier to individualize scan protocols (2, 14). These do not require any intervention from the radiographer and are thus less time consuming.

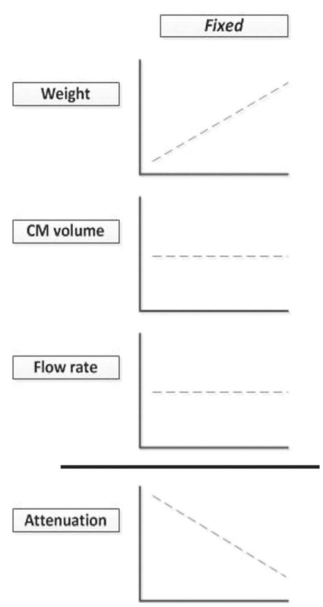
In addition to ATCM and ATVS, iterative reconstruction (IR) techniques are commonly used, primarily to reduce radiation dose. IR reduces image noise by repetitive calculation during reconstruction. Repetition is stopped after completion of a predefined number of cycles, or when the difference between two IR steps has become smaller than a predefined value (15).

A user set image quality for a standard patient is the reference basis for the image quality level in each patient. When using ATCM and ATVS, user set image

quality is determined by reference tube current (mAs_{ref}) and reference tube voltage (kV_{ref}). Furthermore, increasing IR strength is related to a decrease in image noise. Various mAs_{ref} and kV_{ref} values and IR strengths are used in daily clinical practice (16-19). The main goal is to define optimal settings for reaching diagnostic image quality at lowest possible radiation dose.

In contrast-enhanced CT scans CM injection protocols can be adapted to achieve diagnostic image quality at lowest possible CM dosage. The most decisive parameter to base CM injection protocols on is iodine delivery rate (IDR) for vascular studies, and total CM volume for parenchymal studies (20). IDR (gI/s) can be calculated using CM concentration (in mg/ml) multiplied by the CM injection flow rate (in ml/s). In most hospitals a single CM concentration is used, and it is therefore straightforward to adapt flow rate to modify IDR (20).

Figure 1. When contrast (CM) volume and flow rate are kept constant, attenuation of the liver parenchyma is determined by body weight.



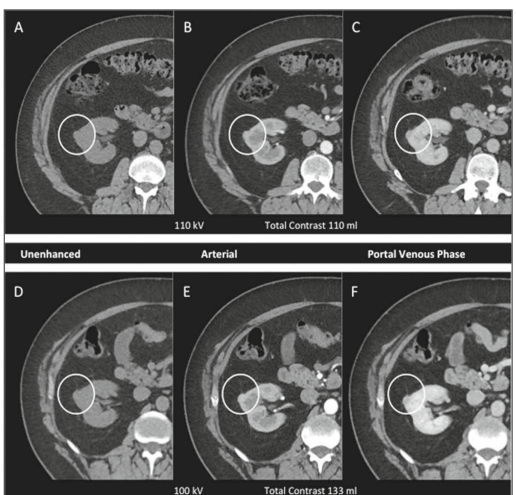
For abdominal imaging, a 'one size fits all' CM injection protocol is used in many centres, i.e. all patients receive the same amount of CM. As a consequence, CM dose is only optimal in a small selection of the patient population (figure 1): patients with lower body weight may receive excess total CM volume which

may lead to very high attenuation and artifacts, whereas heavier patients may receive an insufficient amount of CM for adequate attenuation of the organs. In recent years, different body size indices have been proposed to individualize CM injection protocols. Of these, total body weight is the easiest, measured for example in the scanner room using a calibrated weighing scale. Lean body weight (LBW, i.e. total body weight minus fat), and body surface are (BSA), require more complicated calculations (21-27). Previous studies have shown that body weight adapted CM protocols result in more homogeneous enhancement of both pulmonary and coronary arteries, compared to a 'one size fits all' protocol (28, 29), which may be similarly applicable to abdominal imaging. Furthermore, individualized protocols for coronary and pulmonary arteries resulted in an overall reduction in CM volume for patients with lower body weight (28, 29). A relatively easy way to individualize CM injection protocols is using dedicated CM injection software based on the non-linear relationship between body weight and scan duration (28, 29). The flow rate then depends on the total amount of CM required based on patient body weight (28, 30).

Radiation dose parameters and CM injection protocols cannot be seen as separate entities. This is because tube voltage influences attenuation of iodine (31). When the tube voltage reaches the 33 keV k-edge of iodine, the chance an electron will be dislodged from the k-shell increases, with an increase in photo-electric energies as a result. Therefore, attenuation of iodine increases with decreasing tube voltage and consequently, influencing the one may require adjusting the other. Figure 2 is an example of a patient with a small enhancing kidney lesion, who undergoes regular CT scans for follow-up. The figure shows attenuation of the lesion on an unenhanced CT scan and after injection of iodinated CM. The large differences in attenuation between scans can be attributed to both the lower tube voltage and the larger CM volume used in the second scan. The diagnosis of a malignant kidney lesion depends on CM enhancement (> 15 Hounsfield Units [HU] enhancement in arterial phase compared to the unenhanced phase is suggestive of a renal cell carcinoma), which illustrates the importance of taking both radiation and CM injection protocol into account when acquiring and reading such images (32, 33).

Many studies focus on optimizing either radiation dose or CM injection protocols, which, due to the strong connection between the two, is of limited use without a rule of thumb to match them (6-10, 28, 29, 31).

Figure 2. Images of two repeat scans. (A,B,C and D,E,F) of an enhancing lesion in the right kidney. The two scans were done a year apart and using different scan parameters. Because 100 kV is closer to the 33 keV k-edge of iodine, attenuation of iodine is increased in the second scan. It is surprising therefore that a larger CM volume was used.



	First scan	Second scan
Scanner	Somatom Force	Somatom Force
Tube voltage (kV)	110	100
Weight (kg)	130	130
Contrast volume (ml)	110	133
Total Iodine Load (gI)	33.0	39.9
Dosing factor (gI/kg)	0.254	0.307
Unenhanced CT (HU)	32.9	35.9
Arterial CT (HU)	99.1	132.5
PvP CT (HU)	79.7	97.9

An incentive to such a rule was provided for vascular studies by Kok et al. (34). They used a circulation phantom to demonstrate that when a tube voltage reduction of 120 to 100 kV was accompanied by a 12 % reduction in CM dose, sufficient attenuation of the coronary arteries was achieved (> 325 HU). These results were confirmed in a small patient group (34). The hypothesis may be extended to parenchymal studies. Based on the literature, a tube voltage reduction of 10 kV accompanied by a 10 % reduction in CM volume may result in homogeneous enhancement of the liver, regardless of tube voltage used (23, 35). Even better would be the use of a dosing factor in g I/kg body weight

instead of CM volume: a 10 kV reduction accompanied by a 10 % decrease in dosing factor and vice versa (35). Such a rule of thumb has not yet been evaluated in a clinical setting, however.

There are pitfalls to reducing radiation and CM dose. Excessive radiation dose reduction may lead to increased image noise and result in a non-diagnostic scan (36). At best a non-diagnostic scan may need to be repeated, at worst it may result in underdiagnosis. Small liver lesions not visible due to image noise, for example, could have a large impact on patient treatment and survival. Similarly, a large number of clinical questions require the use of intravenous iodinated CM. Controversy remains on whether the post-contrast acute reduction in renal function sometimes seen reflects kidney injury caused by iodinated CM (37-40). Regardless, lowering CM dose is preferable especially in patients with reduced renal function, and there is simply no reason to give any patient more CM than necessary for diagnostic purposes. The question is, how low can we go without compromising diagnostic image quality?

Diagnostic image quality seems straightforward, while in truth it is quite a difficult concept. Image quality can be assessed objectively or subjectively. Objective image quality encompasses attenuation in HU, the signal to noise ratio (SNR) and the contrast to noise ratio (CNR). SNR is calculated by dividing the attenuation of the target organ by its standard deviation (SD), while CNR is the difference between the attenuation of the organ and the paraspinal muscle, divided by the SD of the same muscle (8, 29, 41, 42). These measurements are quite easy but thresholds are not always well defined: for abdominal imaging a wide variety of acceptable values are found in literature. For subjective image quality the picture is even less clear. The introduction of IR techniques in daily clinical practice has tremendously changed subjective image quality assessment (43), and no clear-cut values exist (9, 10, 44-47). Subjective image quality is often rated on a 5-point Likert scale (e.g. 1, excellent; 2, good; 3, moderate; 4,poor; 5, very poor) (48), but it remains a subjective score influenced by the individual radiologist's preference. Dividing the subjective image quality parameter into smaller units (e.g. noise, contrast, lesion detectability), may improve uniformity. However, in practice image quality is more than just the sum of those parameters. It is clear that both objective and subjective

parameters have their limitations, but no better alternative has been proposed yet, and at this time we have to work with what we've got.

Image quality being so difficult to capture with one reliable parameter, studies would profit from intra-patient comparisons. However, for obvious ethical and ALARA-related principles, this is not possible. In the current era, where artificial intelligence (AI) techniques are emerging, reconstruction software might be of assistance. Using dedicated post-processing software able to mimic lower tube current by inserting noise to the CT image, studies have shown that a radiation dose reduction of 41 to 84 % was possible in CT angiography of various vascular structures in head and neck, without compromising diagnostic image quality (49, 50). No studies have done pairwise comparisons of different radiation doses and IR strengths in abdominal imaging within the same patient, and whether a dose reduction still leads to sufficient image quality in this setting begs to be investigated.

Age and kidney function may affect radiation dose and contrast volume protocol considerations. In a younger patient, reducing radiation dose is important to decrease lifetime attributable cancer risk (3-5), whereas in the older population, where reduced kidney function is more common, a CM dose reduction may be more important (3-5, 37-40). In ATVS, settings (slider level) can be adjusted to optimize either radiation dose or CM (51). In daily clinical practice, the slider is set according to the type of CT performed (e.g. vascular, parenchymal or unenhanced). For each slider setting, a user set reference image quality is specified, based on the CNR. In vascular studies, CM is leading and in general more noise is accepted so that radiation dose can be lower, and a slider position 11 is chosen. For parenchymal studies a balance between attenuation and noise is preferred and the slider is set at position 7. Unenhanced scans use position 3, in which the CNR is based solely on the fat-water contrast (51). Adapting either radiation dose (by changing tube voltage) or CM volume based on age and/or kidney function may be preferable in further optimizing scan and CM injection protocols. Euler et al. showed that this was feasible in vascular CT's, resulting in comparable objective and subjective image quality (51). However, vascular studies have other requirements than parenchymal studies, and slider position manipulation needs to be explored in the setting of abdominal imaging.

Whereas scan and CM injection protocols have been extensively studied, one basic parameter is still under debate: CM temperature. The European Society of Urogenital Radiology (ESUR) and American College of Radiology (ACR) guidelines differ in their recommendations regarding the necessity to prewarm CM prior to injection: ESUR advises standard pre-warming whereas ACR states warming may only be helpful in certain specific circumstances. Increasing CM iodine concentration increases its viscosity, pre-warming CM decreases its viscosity (52-56). It was long thought that injecting CM at a high flow rate (> 6 ml/s) resulted in decreased patient comfort and increased risk of CM extravasations. Patient comfort is important not only for the patient but also for the procedure. An uncomfortable patient might start moving or shivering, breathe more quickly and/or have a faster heartbeat, all of which negatively influence image quality. The EICAR trial showed that injecting iodinated CM with a flow rate as high as 8.3 ml/s is safe and does not increase the risk of CM extravasations and/or pain when CM is pre-warmed to 37° C (99° F) (52). On the other hand, Davenport et al. suggest that pre-warming CM is not necessary for low iodine concentrations. In their study a total of 12.682 pre-warmed injections and 12.138 injections at room temperature were retrospectively evaluated with regard to CM extravasations and adverse events (57). The results were not conclusive: although it is safe to inject CM at room temperature, it could result in a decreased patient comfort and pain. With regard to the individualization, optimalization and efficiency of daily clinical practice, it would be valuable to know whether pre-warming CM is effective in reducing CM adverse events and increasing patient comfort.

Automated systems play a large role in radiation dose optimization (ATCM and ATVS), but CM administration is still often a manual action. To easily, quickly and reliably individualize both radiation and CM, it would be preferable that CM injection protocols be built into the system, linked to the scanner. In that respect, AI might be helpful. AI could help selecting the optimal CM injection protocol for an individual patient on a particular scanner and for a specific scan indication, improving patient care and workflow. Even factors such as patient anxiety and difficulty gaining venous access, which may extend the duration of a scan, could be taken into account for patients having a CT appointment on a regular basis (e.g. oncological follow-up), improving the lead time (58).

Ultimately AI might be able to help in reducing CM volume, scan time, and radiation dose (59).

The aim of this thesis is to optimize and individualize CT protocols for abdominal imaging. The ultimate goal is to provide a combined protocol tailored to both individual patient parameters and clinical question.

OUTLINE OF THIS THESIS

In **Chapter 2** image quality (objective and subjective) is compared between body weight-adapted and standard CM-volume injection protocols.

In **Chapter 3** the relationship between tube voltages and CM injection protocols is studied for abdominal portal venous phase imaging in a randomized controlled trial. A reduction in tube voltage leads to an increase in attenuation of iodine, and therefore may enable a reduction in CM dose.

In **Chapter 4**, optimal reference tube current and IR strength for abdominal imaging is investigated using dedicated simulation software for offline reconstruction of CT images based on raw-data sets.

Where previous chapters evaluate individualized scan protocols based on body weight and tube voltage, **Chapter 5** details a feasibility study in which radiation and CM injection protocols are adjusted to take age and renal function into account.

Chapter 6 reports the results of a randomized controlled trial comparing patient comfort and image quality between protocols using pre-warmed or room temperature CM.

Chapter 7 provides a summary of the most important parameters in both parenchymal and vascular CT imaging. An easy-to-use rule of thumb is proposed that can be applied to individualize CM injection protocols based on both patient body weight and tube voltage.

In **Chapter 8** a comprehensive overview of recent developments in optimizing scan and CM injection protocols is given. With the arrival of AI, new possibilities arise for further radiation and CM dose reductions in the near future. Although the chapter focuses on the coronary arteries, proposed techniques may be applicable to a much broader field.

Chapter 9 contains a general discussion of all previous chapters and future perspectives.

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CHAPTER 2

Individually body weight–adapted contrast media application in computed tomography imaging of the liver at 90 kVp

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Abstract

Objectives: The aim of the present study was to evaluate the attenuation and image quality (IQ) of a body weight adapted contrast media (CM) protocol compared to a fixed injection protocol in computed tomography (CT) of the liver at 90 kV.

Materials and Methods: 199 consecutive patients referred for abdominal CT imaging in portal venous phase were included. Group 1 (N =100) received a fixed CM dose with a total iodine load (TIL) of 33 g I at a flow rate of 3.5 ml/s, resulting in an iodine delivery rate (IDR) of 1.05 g I/s. Group 2 (N = 99) received a body weight adapted CM protocol with a dosing factor of 0.4 g I/kg with a subsequent TIL adapted to the patients' weight. Injection time of 30 s was kept identical for all patients. Therefore, flow rate and IDR changed with different body weight. Patients were divided into three weight categories; ≤ 70 kg, 71 - 85 kg and ≥ 86 kg. Attenuation (HU) in three segments of the liver, signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) were used to evaluate objective IQ. Subjective IQ was assessed by a 5-point Likert scale. Differences between groups were statistically analysed ($p < 0.05$ was considered statistically significant).

Results: No significant differences in baseline characteristics were found between groups. The CM volume and TIL differed significantly between groups ($p < 0.01$), with mean values in group 1 of 110 ml and 33 g I; and in group 2 of 104.1 ± 21.2 ml and 31.2 ± 6.3 g I, respectively. Flow rate and IDR were not significantly different between groups ($p > 0.05$). Body weight adapted protocolling led to more homogeneous enhancement of the liver parenchyma compared to a fixed protocol with a mean enhancement per weight category in group 2 of; 126.5 ± 15.8; 128.2 ± 15.3 and 122.7 ± 21.2 HU, compared to 139.9 ± 21.4; 124.6 ± 24.8 and 116.2 ± 17.8 HU in group 1, respectively.

Conclusions: Body weight adapted CM injection protocols result in more homogeneous enhancement of the liver parenchyma at 90 kV in comparison to a fixed CM volume with comparable objective and subjective IQ, while overall CM volume can be safely reduced in more than half of patients.

Keywords

Multidetector Computed Tomography; Diagnostic Imaging; Liver; Radiation Dosage; Contrast Media

Introduction

Contrast enhanced computed tomography (CT) is frequently used to detect liver lesions and to (sub-)classify liver tumours (1-4). Studies show that hepatic enhancement of ≥ 50 HU is considered necessary to ensure an appropriate visibility of low-attenuating lesions (5-9). Usually, a standard fixed contrast media (CM) volume is used independent of specific patient characteristics such as height, weight, liver status (e.g. cirrhosis and steatosis) and cardiac function (6, 10, 11). All these factors have a direct influence on liver enhancement and, as a result, on lesion visibility. A fixed CM dose therefore results in reduced attenuation levels in the liver in heavier weighted patients, in comparison to patients with a lower total body weight (TBW) (12). As a consequence, this might even lead to scans with an insufficient attenuation resulting in a non-diagnostic CT-scan (12). Alternatively, patients with a low TBW might receive more CM than necessary for sufficient liver attenuation, which is not preferable either (13).

Dedicated CM injection software (P3T™ [Bayer Healthcare, Berlin, Germany]) individualizes CM application for each patient based on body weight and the linear relationship between weight and flow rate (ml/s). As a result, the flow rate and the resulting iodine delivery rate (IDR) differ with a changing TBW. Injection time is constant for all patients. A higher TBW therefore, results in a higher flow rate, with a subsequent increase in total iodine load (TIL). The advantage of an individualized CM injection protocol over a fixed CM injection protocol has already been established in various CT angiography (CTA) studies (14-18). The effects on parenchymal enhancement however, have not been fully investigated, especially in the light of low kV scanning and recent advances in image reconstruction (e.g. iterative reconstruction) (19).

Scanner improvements aid CM volume optimization for each patient. Recent technical advances allow for CT scans to be performed at tube voltages as low as 70 kV, which decreases radiation dose significantly (20-22). In addition,

reducing the tube voltage increases CM enhancement, as the x-ray output comes closer to the 33 keV k-edge of Iodine, which increases (liver) attenuation. This facilitates reduction of CM volume whilst decreasing radiation dose (23, 24). Most previous research on the topic of TBW and liver attenuation has been performed at a fixed tube voltage setting of 120 kV (6, 25, 26). Until now, most thorough studies were performed in an Asian population, with a lower mean TBW than an average European or American population (6, 25-28).

The aim of this study was to establish a possible benefit of individualized CM injection over a fixed CM volume in liver imaging, when applying modern scanner techniques in image acquisition (90 kV protocolling) and post-processing (raw-data based iterative reconstruction methods) in a (heavier) European population.

Materials and Methods

Ethics

The local ethical committee and institutional review board provided a waiver of written informed consent for the study design, as the data was analysed anonymously in accordance with the Institutional Review Board guidelines (METC, ref. 16-4-161).

Study population

All abdominal CT scans in portal venous phase or in combination with a thoracic CTA in patients ≥ 18 years of age, were eligible for inclusion. Patients were excluded in case of hemodynamic instability and general exclusion criteria for contrast enhanced CT were applied (e.g. pregnancy, renal insufficiency [eGFR, 30 ml/min/1.73 m^2], iodine allergy). Technicians asked the patients' weight prior to the scan. In case of doubt, a weighing scale was available. Patients were excluded when the inserted intravenous catheter was not capable of reaching the necessary flow rate for the individualized CM injection, or when injection data was not complete (n = 17). Two patients were excluded because of CM extravasation. In total, 199 consecutive patients were enrolled between November 2017 and May 2018.

Imaging protocol

All scans were performed on a 3rd-generation dual-source CT (DSCT) scanner (Somatom Force, Siemens Healthineers, Forchheim, Germany). Scan range was set from approximately 2 cm cranial of the diaphragm to the pubic symphysis. Scan parameters were as follows: tube voltage was 90 kV, 192 x 0.6 mm slice collimation, gantry rotation time of 0.5 s and a quality reference tube current of 295 mAs_{ref} (CareDose 4D™, Siemens). Image reconstruction was performed in the axial, coronal and sagittal plane with 3 mm slice thickness and 2 mm increment using a Br40 kernel (Advanced Modelled Iterative Reconstruction [ADMIRE], strength 2).

Contrast media injection protocol

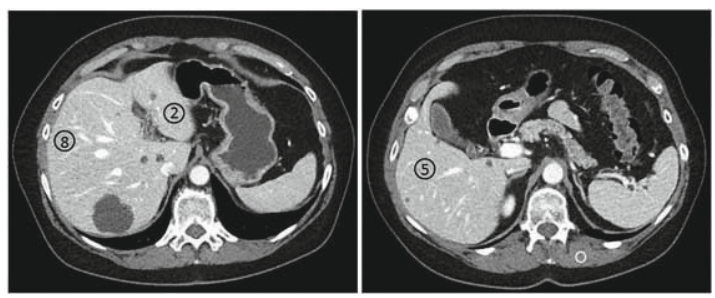
All patients received pre-warmed CM (37 °C [99 °F]) (Ultravist®, Iopromide 300 mg/ml; Bayer Healthcare, Berlin, Germany). All scans were performed in the portal venous phase with a fixed scan delay of 70 s after CM administration, or approximately 35 s after the arterial phase of the thorax. For the latter, delay was calculated by means of bolus tracking, whereas the abdominal scan was performed after an average of 70 s after the start of the CM injection. CM was administered using a programmable dual-head CT power injector (Stellant®; Bayer) and injected through an 18, 20 or 22 Gauge needle, or through a central line.

Group 1 received a standard fixed CM volume of 110 ml (TIL: 33 g I), with a flow rate of 3.5 ml/s (IDR: 1.05 g I/s) followed by a saline flush of 40 ml at the same flow rate.

Group 2 received a body weight adapted CM injection protocol as determined by contrast injection software (P3T™), which consisted of a CM phase followed by a saline flush of 40 ml at the same flow rate (maximum flow rate: 6 ml/s). The individually tailored CM injection software calculates the TIL and flow rate for each patient, depending on body weight. The dosing factor was 0.4 g I/kg and injection time was 30 seconds for all patients (14, 15).

A dedicated data acquisition program (Certega™ Informatics Solution; Bayer) continuously monitored and collected all injection parameters (e.g. total amount of CM [ml] and peak flow rate [ml/s]).

Figure 1. ROIs were drawn in segment 2, 5 and 8 of the liver (when available). The white circle indicates the ROI drawn to determine HU in a paraspinal muscle to determine CNR. (ROI, region of interest; CNR, contrast-to-noise ratio)



Objective image quality

Image quality (IQ) was evaluated by measuring the attenuation (HU) in the liver parenchyma, signal-to-noise (SNR) and contrast-to-noise (CNR) ratio. One experienced researcher (B.M.) measured attenuation values by manually delineating regions of interest (ROIs) within the liver parenchyma. Segments 2, 5 and 8, according to the Couinaud distribution, were used where possible (figure 1) (29). In case liver surgery was performed, the adjacent segment was chosen. An ROI was drawn in each segment (≥ 1 cm^2) without involvement of bordering vascular structures. SNR was calculated by dividing the attenuation of the liver parenchyma by the corresponding standard deviation (SD) of the attenuation (30-34). The attenuation of the left erector spinae muscle was measured at the level of the liver, in order to calculate CNR using the following established formula: liver segment attenuation minus intramuscular attenuation, divided by the SD of the intramuscular attenuation (16, 31-36).

Subjective image quality

Two radiologists (C.M. and B.M.), respectively with 8 and 3 years of experience in abdominal radiology, evaluated the subjective IQ in consensus while blinded

to the injection protocol. Subjective IQ was assessed by using a 5-point Likert scale [1 = excellent; 2 = good; 3 = moderate; 4 = poor; 5 = very poor] (37).

Statistical Analysis

The Kolmogorov-Smirnov test was used to check for normal distribution. Continuous variables were reported as mean ± SD for normally distributed variables. Differences between groups were analysed with the unpaired samples T-test or a one-way analysis of variance (ANOVA) with a Tukey test for post hoc comparison, depending on the number of groups. For non-normally distributed variables, the Mann-Whitney U or Kruskal-Wallis test was performed. Categorical variables were reported as the number of cases and the percentages per group, the X^2 test was used to calculate differences between these groups. Statistic software (SPSS, version 24.0, IBM Corp., New York, NY) was used for the data analysis. All *p*-values were two-sided and a *p*-value below 0.05 was considered statistically significant.

Results

Baseline characteristics

The baseline characteristics of the study population are depicted in table 1 for both groups. No significant differences in baseline characteristics were found between groups.

Table 1. Baseline characteristics. No significant differences were found between groups. (BMI, body mass index; Abd/Th - Abd, Abdominal scan / Abdominal scan with a thoracic CT)

Patient Characteristics	Group 1 (N = 100)	Group 2 (N = 99)	*p*-value
Excluded patients	4	15	
Age (years)	64.2 ± 16.1	64.5 ± 14.5	0.841
Sex (% male)	52 (52 %)	53 (54 %)	0.828
Body weight (kg)	77.1 ± 15.5	77.9 ± 15.9	0.713
Height (m)	1.70 ± 0.09	1.72 ± 0.09	0.188
BMI (kg m^{-2})	26.5 ± 4.3	26.3 ± 4.7	0.716

Table 1. Continued

Patient Characteristics	Group 1 (N = 100)	Group 2 (N = 99)	*p*-value
Scan indication			
Oncology	79 (79 %)	81 (82 %)	0.658
Infectious	7 (7 %)	4 (4 %)	
Other	14 (14 %)	14 (14 %)	
Scan protocol (Abd/Th - Abd)	52 % / 48 %	55 % / 46 %	0.719
Needle Size			
18 Gauge	4 (4 %)	6 (6 %)	0.828
20 Gauge	86 (86 %)	86 (87 %)	
22 Gauge	1 (1 %)	1 (1 %)	
Missing data	9 (9 %)	6 (6 %)	

Injection parameters

Table 2 depicts the injection parameters per group and per weight category, as all patients were divided into three weight categories; ≤ 70 kg, 71 - 85 kg and ≥ 86 kg.

Table 2. Injection parameters. (CM, contrast media; IDR, iodine delivery rate; TIL, total iodine load)

		N	CM volume (ml) ± SD	TIL (g) ± SD	Flow rate (ml/s) ± SD	IDR (g I/s) ± SD	Grams of Iodine per kg
Group 1	***≤ 70 kg***	36	110	33	3.5	1.05	0.55 ± 0.05
	71 - 85 kg	36	110	33	3.5	1.05	0.42 ± 0.02
	≥ 86 kg	28	110	33	3.5	1.05	0.35 ± 0.03
Group 2	***≤ 70 kg***	35	82.4 ± 9.2	24.7 ± 2.8	2.7 ± 0.3	0.82 ± 0.1	0.4
	71 - 85 kg	35	104.3 ± 5.3	31.3 ± 1.6	3.4 ± 0.2	1.03 ± 0.1	0.4
	≥ 86 kg	29	130.0 ± 12.6	38.9 ± 3.4	4.2 ± 0.4	1.28 ± 0.1	0.4
p*-value *Group 1 and 2			< 0.01	< 0.01	0.356	0.448	< 0.01

Figure 2 sets out the CM volume against weight for both groups. The mean CM volume for group 2 was 104.1 ± 21.2 ml (range: 60.3 - 165.3 ml), which was significantly lower than the CM volume in group 1 (110 ml) ($p < 0.01$). A CM volume below 110 ml was used in 65.7% of the patients in group 2.

Figure 2. CM volume set out to weight for each group. Group 1 received a fixed CM volume of 110 ml. Group 2 received a CM volume based on total body weight. (CM, contrast media)

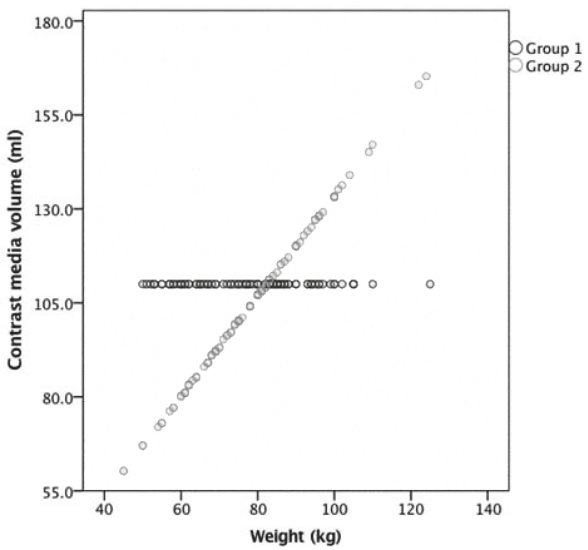


Table 3. Mean effective mAs, $CTDI_{vol}$ (mGy) and DLP (mGy*cm) shown per group and weight category. Values increase with an increasing weight and no significant differences were found between groups. ($CTDI_{vol}$, CT dose $index_{vol}$; DLP, dose length product)

		Mean Effective mAs ± SD	Mean $CTDI_{vol}$ (mGy) ± SD	Mean DLP (mGy*cm) ± SD
Group 1	***≤ 70 kg***	161.6 ± 37.3	4.7 ± 1.1	217.2 ± 58.5
	71 - 85 kg	222.4 ± 78.1	6.3 ± 2.4	311.7 ± 105.4
	≥ 86 kg	239.5 ± 65.0	6.9 ± 1.9	351.2 ± 105.5
	Mean	205.3 ± 70.2	5.9 ± 2.1	288.7 ± 106.4
Group 2	***≤ 70 kg***	158.2 ± 42.1	4.6 ± 1.2	208.9 ± 50.4
	71 - 85 kg	203.7 ± 39.9	5.9 ± 1.2	285.3 ± 59.7
	≥ 86 kg	260.6 ± 102.7	7.5 ± 3.0	379.5 ± 145.5
	Mean	204.3 ± 76.7	5.9 ± 2.2	285.9 ± 113.5
Group 1 vs Group 2	*p*-value	0.969	0.799	0.950

Radiation dose

Mean effective mAs (mAs_{eff}), CT dose $index_{vol}$ ($CTDI_{vol}$) and dose length product (DLP) for group 1 were 205.3 ± 70.2 mAs_{eff}, 5.9 ± 2.1 mGy and 288.7 ± 106.4 mGy*cm, respectively. In group 2, mean values were 204.3 ± 76.7 mAs_{eff}, 5.9 ± 2.2 mGy and 285.9 ± 113.5 mGy*cm. No significant differences were found between groups (table 3).

Table 4. Attenuation value (HU), signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) for each group, shown per weight category. No significant differences in HU, SNR or CNR were found between the two groups. Although for group 1, the attenuation differed significantly between certain weight groups as mentioned below. (HU, Hounsfield Units; SNR, signal-to-noise ratio; CNR, contrast-to-noise ratio).

		Mean HU ± SD	Mean SNR ± SD	Mean CNR ± SD
Group 1		127.8 ± 23.7	8.5 ± 2.5	5.6 ± 2.9
Group 2		126.0 ± 17.4	8.2 ± 1.6	5.4 ± 2.1
p-value		0.536	0.369	0.518
Group 1	***≤ 70 kg***	139.9 ± 21.4	10.4 ± 2.1	6.6 ± 2.7
	71 - 85 kg	124.6 ± 24.8	8.0 ± 2.1	5.5 ± 3.3
	≥ 86 kg	116.2 ± 17.8	6.6 ± 1.4	4.2 ± 1.8
	p-value	< 0.01[1]	< 0.01[2]	< 0.01[3]
Group 2	***≤ 70 kg***	126.5 ± 15.8	9.2 ± 1.2	6.0 ± 1.7
	71 - 85 kg	128.2 ± 15.3	8.3 ± 1.1	5.8 ± 2.1
	≥ 86 kg	122.7 ± 21.2	6.9 ± 1.7	4.3 ± 2.0
	p-value	0.450	< 0.01[2]	< 0.01[4]

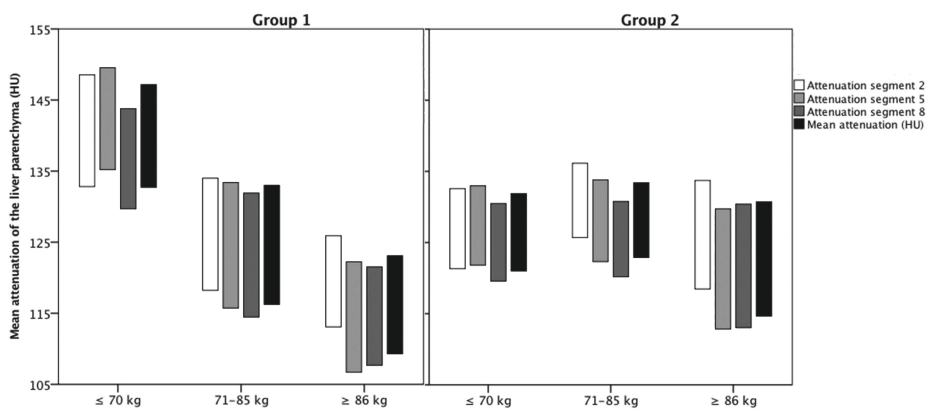
[1] Post hoc comparison showed a significant difference between weight category ≤ 70 kg and 71 - 85 kg; and ≤ 70 kg and ≥ 86 kg.
[2] Post hoc comparison showed a significant difference between all three weight categories.
[3] Post hoc comparison showed a significant difference between weight category ≤ 70 kg and ≥ 86 kg.
[4] Post hoc comparison showed a significant difference between weight category ≤ 70 kg and ≥ 86 kg; and 71 - 85 kg and ≥ 86 kg.

Objective image quality

For group 1 mean attenuation values of the liver parenchyma for each weight category (≤ 70 kg; 71 - 85 kg; ≥ 86 kg) were 139.9 ± 21.4 HU; 124.6 ± 24.8 HU and 116.2 ± 17.8 HU. A significant difference in attenuation was found between

the lowest and the middleweight category and between the lowest and highest weight group. In contrast, group 2 attenuation values were comparable and not significantly different between the three weight groups; 126.5 ± 15.8 HU; 128.2 ± 15.3 HU and 122.7 ± 21.2 HU, respectively (*p* = 0.450, table 4 and figure 3). The mean SNR and CNR were not statistically different between group 1 and group 2 (*p* = 0.369 and 0.518, respectively) (table 4). The mean SNR for group 1 and 2 was 8.5 ± 2.5 (range: 1.9 - 14.5) and 8.2 ± 1.6 (range: 3.5 - 11.7). For CNR, mean values were: 5.6 ± 2.9 (range: -5.4 - 16.8) and 5.4 ± 2.1 (range: 0.7 - 11.9) for group 1 and 2.

Figure 3. Attenuation of the liver parenchyma in segment 2, 5, 8, according to the Couinaud distribution (29). When liver surgery was performed, the adjacent segment was chosen. Attenuation is set out per weight category for both group 1 and group 2.



Subjective Image quality

The subjective IQ was diagnostic in all scans, ranging from average to excellent with no significant difference between groups (*p* = 0.213) (table 5). No significant differences in subjective IQ between the weight categories were found in both group 1 and group 2 (*p* = 0.076 and 0.358, respectively).

Table 5. Subjective IQ rated on a 5-point Likert scale for both groups. (IQ, image quality)

	Excellent	***Good***	***Average***	***Poor***	***Very Poor***
Group 1	25 (25.0 %)	63 (63.0 %)	12 (12.0 %)	0 (0.0 %)	0 (0.0 %)
Group 2	15 (15.2 %)	72 (72.7 %)	12 (12.1 %)	0 (0.0 %)	0 (0.0 %)

Discussion

An individualized CM injection protocol tailored to TBW resulted in a more homogeneous enhancement of the liver parenchyma in comparison to the fixed CM volume injection protocol (figure 3). In the latter, a steady decline of liver enhancement with increasing TBW was observed.

In the portal venous phase, CM volume and TIL are the most important factors determining liver enhancement. Flow rate and IDR are less important, unlike in CTA where those parameters are most influential (12, 23). Due to the nature of our study design, CM volume and TIL are significantly different between group 1 and 2, while values for flow rate and IDR are comparable between both groups ($p > 0.05$) (table 2). The individualized protocol resulted in a CM volume reduction for nearly two third of our patients while ensuring similar IQ.

The standard deviation is smaller in group 2, which is also an indication for a more homogeneous attenuation of the liver parenchyma. Interestingly, the highest weight category shows a similar standard deviation to group 1 and a slightly lower overall attenuation than the other weight categories in group 2. A potential explanation for this finding might be a higher percentage of people with steatosis in the heavier population and therefore a greater spread in attenuation in this category.

Some studies have already established the beneficial effect of using body size parameters to individualize CM injection protocols in liver imaging. However, most previous studies were performed in an Asian population and/or at a tube voltage of 120 kV and/or with filtered back projection (6, 25, 26). Mean TBW in the studies by Kondo et al. and Awai et al. ranged between 53.5 and 57.6 kg (6, 25, 26). Mean CM volume used in those studies was between 107 and 111 ml, with a TIL between 32.1 and 33.3 g I (6, 26). Mean TBW in our population was much higher than the mean body weight in the earlier mentioned Asian studies, while in addition, we were able to use a lower mean CM volume. The use of a standard lower tube voltage in combination with a body weight adapted CM injection protocol and advanced iterative image reconstruction, resulted in nearly a 5 % reduction of CM volume for group 2 compared to the Asian studies.

Administrating too much CM in lighter patients can result in hyper attenuation of the liver parenchyma and an unnecessarily high total injected CM volume. Although this doesn't necessarily lead to inadequate IQ, it is not preferable for the patients. In the heavy patient population however, an insufficient CM volume might result in a decreased detectability of liver lesions.

Recent literature does not describe a clear cut-off value for diagnostic IQ. Mean SNR values range from 4.3 ± 0.6 to 17.9 ± 1.9 and mean CNR ranges between 5.2 ± 2.7 and 6.8 ± 3.0 in recent studies using iterative reconstructions (4, 27, 28, 32, 33, 38, 39). These values show a high degree of divergence and are not comparable between studies, because different scanners, scan techniques and CM injection protocols are used. However, in this study SNR and CNR were not significantly different between both groups and consistent with previous published data. Previous literature states the sole use of parameters such as CNR and SNR might not be a correct representation of the IQ (40, 41). For example, the CNR only depends on contrast and noise. Factors such as the size of a lesion, its shape and the distribution of the CM attenuation within the lesion are not taken in to account. This is considered a shortcoming in currently used methods for determining objective IQ in CT imaging.

Currently, abdominal CT scans in daily clinical routine are performed at lower tube voltages than the former clinical standard of 120 kV. Reducing tube voltage most importantly results in a radiation dose reduction, but also provides the possibility for CM volume reduction. Diagnostic accuracy, however, should be prioritised over radiation dose and CM volume in liver lesion detection. Maximal reduction of radiation and CM volume are of questionable value if the radiologist can no longer differentiate between presence or absence of liver lesions. Higher tube potentials, fuelled by the development of modern scanners, in combination with tube current modulation software ensure that the tube current can be increased to a great extent, guaranteeing a constant IQ (20). However, no research has been performed to prove that this tube voltage and CM volume reduction results in the same IQ and lesion detection potential as the ground rules set out by Heiken et al. (5). Future research should be tailored towards optimization of both radiation dose and CM volume while maintaining diagnostic IQ.

Limitations

This study has several limitations. First, this is a single-centre study, investigating a limited number of patients. In our opinion however, the baseline characteristics are a good reflection of the European population. Secondly, patients reported their own weight and only in case of doubt, a weighing scale was used. Therefore, some discrepancy in patients' weight could have occurred. However, this is a straightforward approach which is comparable to the clinical setting as well. Next, lean body weight has proven to be useful in the Asian population, it would be interesting to investigate this parameter in future studies and compare it to TBW. Fourth, liver diseases (e.g. steatosis and cirrhosis) and other parameters, such as cardiac function, most likely influence liver attenuation to a certain degree. These patients were not excluded here, but assumed to be randomly assigned to both groups. Therefore, it could be interesting to have a closer look into this patient subpopulation, e.g. by analysing delta HU in attenuation between unenhanced and a portal venous phase CT. This delta HU could provide a more constant parameter to determine liver enhancement, compared to HU in portal venous phase solely.

Conclusion

Usage of a body weight tailored CM injection protocol results in more homogeneous liver enhancement at lower tube voltage (e.g. 90 kV) in comparison to a fixed CM injection protocol, while CM volume can be reduced in a large percentage of the population.

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CHAPTER 3

A solution for homogeneous liver enhancement in computed tomography

Results from the COMpLEx Trial

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Abstract

Objectives: The aim of the study was to reach homogeneous enhancement of the liver, irrespective of total body weight (TBW) or tube voltage. An easy to use rule of thumb, the 10-to-10 rule, which pairs a 10 kV reduction in tube voltage with a 10 % decrease in contrast media (CM) dose, was evaluated.

Materials and Methods: Two hundred fifty-six patients scheduled for an abdominal CT in portal venous phase were randomly allocated to one of four groups. In group 1 (n = 64) a tube voltage of 120 kV and a TBW-adapted CM injection protocol was used: 0.521 g I/kg. In group 2 (n = 63), tube voltage was 90 kV and the TBW-adapted CM dosing factor remained 0.521 g I/kg. In group 3 (n = 63), tube voltage was reduced by 20 kV and CM dosing factor by 20 % compared to group 1, in line with the 10-to-10 rule (100 kV; 0.417 g I/kg). In group 4 (n = 66): tube voltage was decreased by 30 kV paired with a 30 % decrease in CM dosing factor compared to group 1, in line with the 10-to-10 rule (90 kV; 0.365 g I/kg). Objective image quality was evaluated by measuring attenuation in Hounsfield units (HU), signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) in the liver. Overall subjective image quality was assessed by two experienced readers by using a 5-point Likert scale. Two-sided p-values below 0.05 were considered significant.

Results: Mean attenuation values in groups 1, 3 and 4 were comparable (118.2 ± 10.0; 117.6 ± 13.9; 117.3 ± 21.6 HU respectively), whereas attenuation in group 2 (141.0 ± 18.2 HU) was significantly higher than all other groups ($p < 0.01$). No significant difference in attenuation was found between weight categories ≤ 80 kg and > 80 kg within the four groups (p ³ 0.371). No significant differences in subjective image quality were found ($p = 0.180$).

Conclusions: The proposed 10-to-10 rule is an easily reproducible method resulting in similar enhancement in portal venous CT of the liver throughout the patient population, irrespective of TBW or tube voltage.

Keywords

Multidetector Computed Tomography; Diagnostic Imaging; Liver; Radiation Dosage; Contrast Media

Introduction

Contrast media (CM) are used in Computed Tomography (CT) scans to enhance vascular structures and organ parenchyma. The visibility of liver lesions depends mainly on image noise and the ratio between size and difference in attenuation of the lesion compared to the parenchyma (1). Comparing the unenhanced parenchyma to that after CM administration (in the same patient), Heiken et al. (1995) found that an attenuation difference (Δ) of at least 50 Hounsfield Units (HU) is necessary to safely detect liver lesions (2). A dosing factor of 0.521 grams of iodine per kg (g I/kg) was proposed to reach the required Δ 50 HU at a given tube voltage of 120 kV (2). By taking the HU of the unenhanced liver into account, a correction can be performed for any liver disorder that might affect background attenuation of the liver.

Parenchymal enhancement depends on scan (e.g. CT scanner, tube voltage), CM (e.g. volume, concentration, flow rate, temperature) and patient characteristics. Relevant patient related parameters include weight, height, venous access, cardiac output, age, gender, breath-hold, renal function and comorbidity (3). Previous research showed that individualized CM injection protocols, where the CM bolus is adapted to patient total body weight (TBW), lean body weight (LBW), or body surface area (BSA), yields better results (1, 4-8). A recent feasibility study demonstrated that a TBW adapted CM injection protocol resulted in more homogeneous liver enhancement compared to fixed iodine load (9).

Recent technological developments in X-ray tube technology permit lower tube voltages whilst maintaining satisfactory image quality, which subsequently leads to lower radiation doses (10, 11). Reducing tube voltage increases attenuation of iodine, by approaching the 33 keV k-edge of iodine. This enables both a reduction of the radiation dose and CM volume (12). This phenomenon, where changing tube voltage influences iodine attenuation, might result in clinical controversies. For example, in imaging of renal masses attenuation

may indicate whether a lesion is more likely benign or malignant (13, 14). When patients are scanned with variable tube voltages iodine attenuation is affected, consequently conclusions cannot be derived from the magnitude of the attenuation. Therefore, it is important to find a method by which the attenuation pattern of parenchymal structures remains robust irrespective of the tube voltage or patient TBW.

In recent literature the importance of individualized CM injection protocols reducing CM volume at a lower tube potential has been stressed in vascular studies (15-17). To the best of our knowledge this has not been investigated in abdominal imaging. This study tested the following hypothesis: a 10 % reduction in CM dosing factor per 10 kV should yield homogeneous enhancement of the liver in portal venous CT, irrespective of TBW and at variable tube voltages (10-to-10 rule) (18, 19).

The aim of the present study was to investigate whether adapting a TBW-based dosing factor to the tube voltage used results in homogeneous liver enhancement between patients.

Materials and Methods

Ethics

This double-blind randomized controlled trial was approved by the local ethics committee as well as by the institutional review board and is registered on ClinicalTrials.gov (NCT02462044). Written informed consent for inclusion in the clinical trial was obtained.

Study population

Patients were enrolled between December 2018 and June 2019 at Maastricht University Medical Center. Patients scheduled for an abdominal CT in the portal venous phase were eligible for inclusion. Possible scan indications were oncology, infection, and screening after incidental findings on ultrasound, weight loss, or abdominal pain. Exclusion criteria were age below 18 years, TBW > 115 kg (because of practical considerations: a CM syringe contains 200 ml),

hemodynamic instability, and general contraindications for contrast-enhanced CT (e.g. pregnancy, renal insufficiency [estimated glomerular filtration rate of < 30 mL/min per 1.73 m^2] and iodine allergy). Scanning additional to the portal venous phase was not a reason for exclusion (other phases: e.g. arterial phase, late phase; other organ region: e.g. combination with thoracic scanning). Patient body weight was measured on calibrated scales in the scanner room and the patient height was asked prior to the CT scan. BMI was calculated by dividing body weight (in kg) by height (in m) squared. Repeat inclusion was not expected to influence study outcome and was therefore allowed.

Patients were prospectively included into one of four groups. A computer random number generator prepared the randomization schedule in a 1:1:1:1 manner (i.e. balanced randomization). Stratification was performed, based on age (< 60 and ≥ 60 years) and weight (< 75 and ≥ 75 kg). Variable block randomization distributed patients equally over the groups.

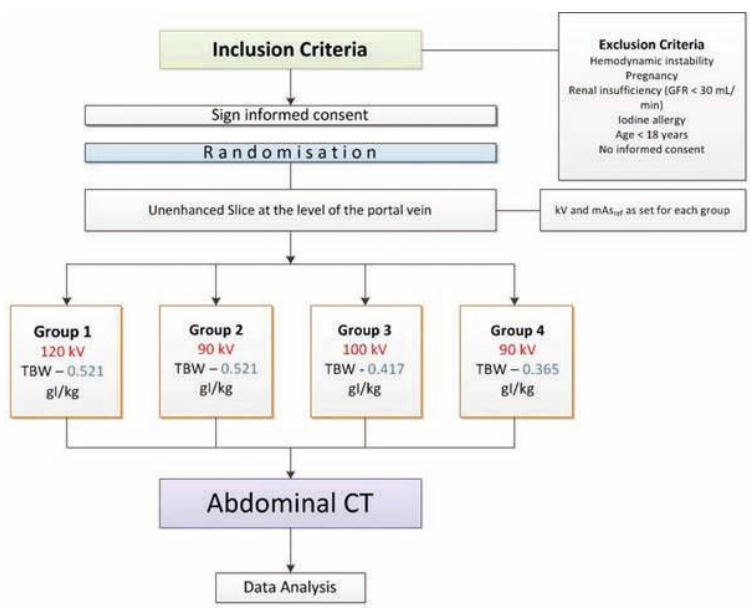
Scan and contrast media protocol

All scans were performed on a third-generation dual-source CT scanner (Somatom Force; Siemens Healthineers, Forchheim, Germany). Automated tube current modulation (ATCM) was used (CareDose 4D; Siemens), while tube voltage was set. A 3 mm slice was scanned at the level of the main portal vein prior to CM administration to establish the baseline attenuation of the unenhanced liver as mentioned in the introduction. Parameters were similar to the subsequent contrast-enhanced scan: tube voltage 120, 100 or 90 kV (depending on the allocated group); slice collimation 192 x 0.6 mm; gantry rotation time 0.5 seconds; quality reference kV and mAs set to respectively 120 kV_{ref} and 150 mAs_{ref}. The abdominal scan range was set from approximately 2 cm above the diaphragm to the pubic symphysis.

Prewarmed CM (37°C [99°F]) was used at a concentration of 300 mg/mL (Iopromide; Bayer Healthcare, Berlin, Germany). CM was injected with a programmable dual-head CT power injector (Stellant, Bayer) through an 18, 20 or 22 gauge needle. Group 1 received the protocol considered the golden standard: 120 kV and 0.521 g I/kg (2). Group 2 received an adapted protocol with CM dosing factor identical to group 1 (e.g. 0.521g I/kg), but tube voltage

reduced to 90 kV. In group 3 tube voltage was set at 100 kV and the dosing factor was reduced by 20 % in accordance with the 10-to-10 rule (e.g. 0.417 g I/kg). Group 4 received a 90 kV scan protocol with a 30 % reduction in dosing factor compared to group 1 in accordance with the 10-to-10 rule: 0.365 g I/kg (figure 1). CM injection duration was 30 seconds in all patients, as determined by dedicated CM injection software (P3T; Bayer Healthcare, Berlin, Germany), and therefore flow rate (in ml/s) was dependent on the weight of the patient and the allocated group (9). The scan in the portal venous phase was performed 70 seconds after start of the CM injection in all patients. CM volume (in ml), total iodine load (TIL, g I), flow rate and iodine delivery rate (IDR, in g I/s) were monitored and collected with a dedicated data acquisition program (Certega™ Informatics Solution; Bayer).

Figure 1. Patients were randomly assigned to one of four groups. An unenhanced slice at the level of the portal vein was scanned before contrast media injection.



Dose-related parameters (e.g. CT dose index [$CTDI_{vol}$, in mGy] and dose length product [DLP, in mGy*cm]) were recorded and collected from the dose sheet available at the PACS workstation (IMPAX version 6.6.1.5003, AGFA HealthCare N.V., Mortsel, Belgium). As mentioned above, all patients scheduled for an abdominal CT in portal venous phase were eligible for inclusion. Therefore, an

additional thoracic scan or other scan phases of the liver were not reasons for exclusion. As a result, three different dose protocols were possible: abdominal scan in portal venous phase, abdominal scan in portal venous phase with a separated arterial thoracic CT, or a thoracic and abdominal scan in portal venous phase. Only the $CTDI_{vol}$ and DLP of the abdominal scan in portal venous phase were collected from the dose sheet. In cases where the thorax and abdomen where scanned together in portal venous phase, the corresponding $CTDI_{vol}$ and DLP were collected.

Image reconstruction was performed with 3 mm slice thickness, with overlapping increment of 2 mm, in an axial, coronal and sagittal plane with a soft tissue kernel (Br40; Siemens; Advanced Modelled Iterative Reconstruction, strength 2 - 3).

Data processing

The objective image quality was evaluated by measuring attenuation (HU) in three different liver segments on both the unenhanced and contrast-enhanced portal venous phase scans, where possible in segments 2, 5 and 8, according to the Couinaud classification (20). If not possible (e.g. previous surgery, large lesions) an adjacent location close to the respective segment was chosen. A region of interest (ROI) was drawn in each liver segment (area: ≥ 1 cm^2), choosing the largest possible ROI area not containing large blood vessels, bile ducts or liver lesions. Dividing the HU of each segment by its standard deviation (SD) resulted in the signal-to-noise ratio (SNR) (21-25). The mean of the measurements in segments 2, 5 and 8 is reported as the SNR. The HU and SD of the left paraspinal muscle at the level of the liver was used to calculate the contrast-to-noise ratio (CNR) as follows: the attenuation of each liver segment minus the attenuation of the left paraspinal muscle, divided by the SD of the attenuation of the paraspinal muscle (9, 22-27). The mean of three CNR measurements is reported.

Two abdominal radiologists (B.M. and C.M.) with respectively 4- and 9-years' experience in abdominal CT, rated the scans in portal venous phase in consensus while being blinded to the protocol. The radiologists were allowed to

adjust window-level settings. Overall image quality was rated on a 5-point Likert scale: 1 = excellent; 2 = good; 3 = moderate; 4 = poor; 5 = very poor (9, 28).

Statistical Analysis

Continuous variables are presented as mean ± SD and categorical variables as absolute numbers with percentages. In order to correct for the possible confounders gender and iterative reconstruction (IR) strength an analysis of covariance was performed, since all variables are continuous. Fifteen patients (5.9 %) were reconstructed with IR strength 3 instead of 2. It was decided not to exclude the scans reconstructed with IR 3 but to statistically correct for this inconvenience instead, as the IR strength does not influence the attenuation of the liver parenchyma, which was our primary outcome (29). This analysis was used for both continuous and ordinal variables, because the steps within the ordinal variables were deemed to be of comparable size. P-values are all 2-sided and considered significant when below 0.05. Statistical software (SPSS, version 24.0; IBM Corp, New York, NY) was used for the data analysis.

Table 1. Baseline characteristics (BMI indicates body mass index).

Patient Characteristics	**Group 1 (N = 64)**	**Group 2 (N = 63)**	**Group 3 (N = 63)**	**Group 4 (N = 66)**
Excluded patients	4	5	4	4
Age (years)	64.0 ± 11.4	66.1 ± 12.6	65.6 ± 8.5	64.3 ± 9.9
Sex (% male)	73.3 %	53.4 %	40.7 %	59.7 %
Body Weight (kg)	79.5 ± 12.7	77.7 ± 14.0	78.5 ± 14.3	79.8 ± 14.8
Height (m)	1.75 ± 0.1	1.71 ± 0.1	1.71 ± 0.1	1.74 ± 0.1
BMI (kg m^{-2})	25.8 ± 3.3	26.5 ± 4.2	26.7 ± 4.3	26.5 ± 4.5
Scan indication				
Oncology (%)	95.0 %	89.7 %	94.9 %	96.8 %
Other (%)	5.0 %	10.3 %	5.1 %	3.2 %
Needle Size				
18 gauge (%)	58.3 %	48.3 %	52.5 %	46.8 %
20 gauge (%)	31.7 %	37.9 %	39.0 %	40.3 %
22 gauge (%)	0.0 %	0.0 %	0.0 %	3.2 %
Missing data (%)	10.0 %	13.8 %	8.5 %	9.7 %

Results

Two hundred fifty-six patients were randomly allocated to one of four groups (group 1, n = 64; group 2, n = 63; group 3, n = 63; and group 4, n = 66) (table 1). Despite randomisation, we observed a difference in gender distribution between groups (% male group 1 = 73.3; group 2 = 53.4; group 3 = 40.7; and group 4 = 59.7). Fifteen patients were excluded: 12 for technical reasons; 2 because only the liver was imaged and therefore radiation doses where not comparable; 1 because of CM extravasation.

Table 2. Data are presented as mean and standard deviation (SD). * Post hoc comparison showed a significant difference between groups 1 and 3; groups 1 and 4; groups 2 and 3; groups 2 and 4; and groups 3 and 4. Only groups 1 and 2 did not significantly differ. (CM indicates contrast media; TIL, total iodine load; IDR, iodine delivery rate; CTDIvol, CT dose index$_{vol}$; DLP, dose length product).

		Group 1 (n = 60)	Group 2 (n = 58)	Group 3 (n = 59)	Group 4 (n = 62)	p-value for difference between groups
CM volume (ml)		138.0 ± 22.0*	135.0 ± 24.3*	109.1 ± 19.9*	97.1 ± 18.0*	< 0.01
TIL (g)		41.4 ± 6.6*	40.5 ± 7.3*	32.7 ± 6.0*	29.1 ± 5.4*	< 0.01
Flow rate (ml/s)		4.5 ± 0.7*	4.4 ± 0.8*	3.6 ± 0.7*	3.2 ± 0.6*	< 0.01
IDR (g I/s)		1.4 ± 0.2*	1.3 ± 0.2*	1.1 ± 0.2*	1.0 ± 0.2*	< 0.01
PvP Abdomen	Number of patients (in %)	13 (21.7 %)	17 (29.3 %)	12 (20.3 %)	15 (24.2 %)	
	$CTDI_{vol}$ (mGy)	7.8 ± 1.0	7.8 ± 1.8	7.9 ± 2.2	6.6 ± 1.7	0.322
	DLP (mGy*cm)	376.9 ± 74.5	339.0 ± 128.4	389.8 ± 136.1	303.2 ± 101.9	0.440
PvP Abdomen + Art. thorax	Number of patients (in %)	18 (30.0 %)	14 (24.1 %)	20 (33.9 %)	22 (35.5 %)	
	$CTDI_{vol}$ (mGy)	7.4 ± 1.2	7.3 ± 2.4	6.5 ± 1.5	8.0 ± 3.2	0.308
	DLP (mGy*cm)	349.7 ± 63.7	360.1 ± 137.8	310.1 ± 67.7	391.9 ± 155.7	0.459
PvP Thorax + Abdomen	Number of patients (in %)	29 (48.3 %)	27 (46.6 %)	27 (45.8 %)	25 (40.3 %)	
	$CTDI_{vol}$ (mGy)	7.0 ± 1.6	6.2 ± 1.8	6.8 ± 2.2	7.0 ± 3.5	0.765

Table 2. Continued

		Group 1 (n = 60)	Group 2 (n = 58)	Group 3 (n = 59)	Group 4 (n = 62)	p-value for difference between groups
	DLP (mGy*cm)	483.8 ± 121.3	386.2 ± 137.4	432.4 ± 131.6	472.2 ± 228.8	0.522
Mean	$CTDI_{vol}$ (mGy)	7.3 ± 1.4	6.9 ± 2.0	6.9 ± 2.0	7.2 ± 3.1	0.405
	DLP (mGy*cm)	420.4 ± 114.9	366.0 ± 134.1	382.3 ± 125.5	402.8 ± 189.2	0.178

Injection parameters and radiation dose

See table 2 for an overview of CM injection parameters. As a result of the study design significant differences were found in CM volume, TIL, flow rate and IDR with p-values < 0.01. Table 2 shows the scan protocols and the mean radiation dose for each group. As expected with identical reference kV and mAs for each group, no significant differences in volumetric $CTDI_{vol}$ or DLP were found between groups, p = 0.405 and p = 0.178, respectively.

Table 3. Mean attenuation (HU), SNR and CNR between groups.

	Group 1 (n = 60)	Group 2 (n = 58)	Group 3 (n = 59)	Group 4 (n = 62)	p-value
Mean HU Unenhanced	60.6 ± 7.2	56.0 ± 11.4	56.2 ± 10.3	53.7 ± 13.5	0.149
Mean HU PvP	118.2 ± 10.0	141.0 ± 18.2	117.6 ± 13.9	117.3 ± 21.6	< 0.01[1]
Mean SNR PvP	9.3 ± 1.6	9.6 ± 1.9	8.8 ± 1.7	8.6 ± 2.1	< 0.01[2]
Mean CNR PvP	5.8 ± 1.8	6.8 ± 2.2	5.4 ± 1.7	5.4 ± 2.7	< 0.01[3]

[1] Post hoc comparison showed a significant difference between groups 1 and 2 (p < 0.01); groups 2 and 3 (p < 0.01); and groups 2 and 4 (p < 0.01).
[2] Post hoc comparison showed a significant difference between groups 1 and 4 (p = 0.016); groups 2 and 3 (p = 0.012); and groups 2 and 4 (p < 0.01).
[3] Post hoc comparison showed a significant difference between groups 1 and 2 (p < 0.01); groups 2 and 3 (p < 0.01); and groups 2 and 4 (p < 0.01).
(HU indicates Hounsfield Units; SD, standard deviation; PvP, portal venous phase; SNR signal-to-noise ratio; and CNR contrast-to-noise ratio)

Objective image quality

The mean HU in the portal venous phase was not significantly different between groups 1, 3 and 4, whereas attenuation in group 2 was significantly higher compared to all other three groups (table 3 and figure 2). Mean HU values in the portal venous phase were 118.2 ± 10.0, 141.0 ± 18.2, 117.6 ± 13.9 and 117.3 ± 21.6 in groups 1, 2, 3 and 4 respectively. A significant difference in HU was found between groups 1 and 2; between groups 2 and 3; and between groups 2 and 4 (all $p < 0.01$). Mean body weight was approximately 80 kg in all groups, and therefore patients were divided in two weight categories (≤ 80 kg and > 80 kg), these were slightly different from the stratification factors used for the randomization process (<75 and ≥ 75 kg). No significant difference in attenuation in the portal venous phase between weight categories was found within groups, with p-values 0.371, 0.925, 0862, and 0.557 for groups 1 through 4 respectively. Figure 2 depicts mean HU values in the portal venous phase, per group and weight category. Mean HU values found for unenhanced slices of the liver at the level of the main portal vein were not significantly different between the four groups ($p = 0.149$).

Mean SNR was highest in groups 1 and 2 (9.3 ± 1.6 and 9.6 ± 1.9 respectively), and significantly higher than the values in groups 3 and 4 (8.8 ± 1.7 and 8.6 ± 2.1 respectively, $p < 0.01$). CNR was significantly higher in group 2 (6.8 ± 2.2), compared to groups 1, 3 and 4 (5.8 ± 1.8, 5.4 ± 1.7 and 5.4 ± 2.7 respectively, $p < 0.01$) (table 3).

Subjective Image quality

Results of the subjective image quality evaluation are presented in table 4. No significant differences were found between groups ($p = 0.180$). All scans were regarded as diagnostic, none of the CT scans were rated of poor or very poor image quality, and image quality was considered good or excellent in 93.7 % of the scans.

Figure 2. Mean attenuation of the liver parenchyma in portal venous phase set out per group and weight category.

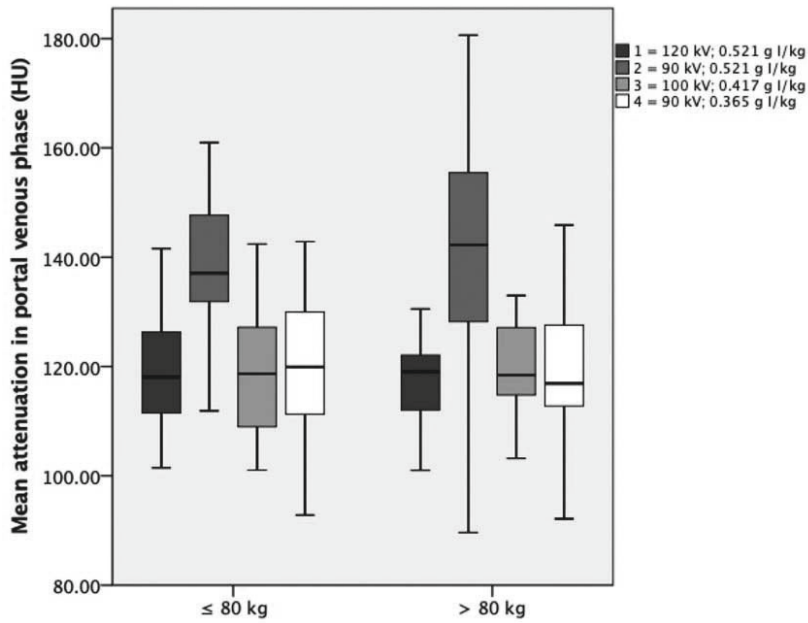


Table 4. Subjective image quality scored in consensus.

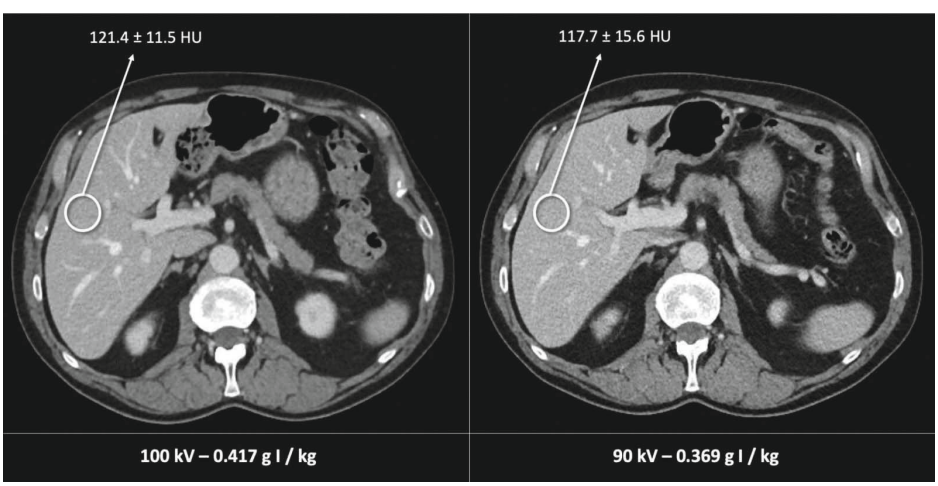
	Group 1 (n = 60)	Group 2 (n = 58)	Group 3 (n = 59)	Group 4 (n = 62)	p-value
Excellent	18 (30.0 %)	9 (15.5 %)	16 (27.1 %)	11 (17.7 %)	
Good	41 (68.3 %)	44 (75.9 %)	38 (64.4 %)	47 (75.8 %)	
Moderate	1 (1.7 %)	5 (8.6 %)	5 (8.5 %)	4 (6.5 %)	0.180
Poor	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	
Very Poor	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	

Discussion

This study showed that an individualized CM injection and scan protocol, where a 10 kV reduction in tube voltage is paired with a 10 % reduction in dosing factor, resulted in homogeneous enhancement of the liver throughout the entire study population. By using this 10-to-10 rule and the CM dosing factor, portal venous abdominal CT protocols can be easily individualized based on tube voltage and patient TBW.

As hypothesized, the 10-to-10 rule results in robust enhancement of the liver at variable tube voltages irrespective of TBW. This is illustrated in figure 3, which shows two scans of a patient who was included twice in the study and allocated to two different scan protocols resulting in similar enhancement of the liver (first allocation to group 4: 90 kV and 0.365 g I/kg; second allocation to group 3: 110 kV and 0.417 g I/kg).

Figure 3. A 57-year old man in the follow up for metastasized urothelial cell carcinoma, included twice and randomized in two different groups. Images were both reconstructed with kernel BR40 and iterative reconstruction (IR) strength 2. The circle indicates the mean Hounsfield Units (HU) measured in three different liver segments (preferable in segment 2, 5 and 8, according to the Couinaud distribution [19]), with the mean standard deviation.



Mean HU values in the portal venous phase were not significantly different between groups 1, 3 and 4, while attenuation was significantly higher in group 2 compared to the other three groups. In addition, when this rule is applied,

a 10 % CM dose reduction can be achieved with every 10 kV tube voltage reduction (figure 2). Mean HU values for the unenhanced slice of the liver were not significantly different between groups and we may conclude that possible factors influencing attenuation of the unenhanced liver (e.g. steatosis and cirrhosis) were not noticeably different between groups and will not unduly influence attenuation in portal venous phase.

CNR was highest in group 2 and comparable between groups 1, 2 and 3 (table 3). The larger variation in SNR values can be explained by the study setup. A higher tube voltage with comparable tube current results in less image noise, while higher CM volumes result in a higher attenuation. Therefore, SNR is, as expected, highest in group 2. In group 4, the lowest tube voltage is used in comparison to the other groups and therefore a slightly lower SNR is expected and observed. SNR values were within the ranges reported in literature (2, 9, 30-32). Furthermore, subjective image quality was considered good or excellent in 93.7 % of the scans.

Numerous studies have explored the possibilities of reducing both CM volume and tube voltage (33-37). To the best of our knowledge, no other study evaluated a rule of thumb to customize both CM and tube voltage and simultaneously individualize the protocol based on TBW in abdominal CT imaging. In this randomized controlled trial, CM injection was individualized based on TBW and no significant differences in attenuation were found between weight categories ≤ 80 kg and > 80 kg (figure 2). Awai et al. showed that LBW might be the more reliable parameter to base the injection protocol on compared to TBW and BSA (8). However, LBW must be calculated using the Boer or the James formula, the first being preferred for heavier patients (28), and this may prove to be too time consuming for daily clinical practice affecting daily clinical routine. Therefore, considering both time and effort, TBW might be more practical. Future research can be directed toward the role of LBW in individualizing scan and CM injection protocols, while taking cost-effectiveness into account.

Nowadays, CT scans are performed at lower tube voltages and most of the scanners incorporate techniques such as ATCM and automated tube voltage selection into their systems, thereby providing an easy method to individualize radiation dose while optimizing image quality. At present, newer CT scanners

are capable of automatically adapting various scan parameters to individual patients, while CM is most often administered in a one size fits all approach. This contradiction is easily explained by the fact that CM administration is still a manual, and therefore a more time consuming, procedure. A connection between scanner and CM injector might be the solution to further individualisation of protocols.

Limitations

This study has several limitations. First of all, in this single-centre study, a difference was found between the number of men and women in the different groups. As this is a randomized controlled trial, it can be attributed to coincidence, but effects on outcome parameters cannot be ruled out. The distribution of fatty tissue is known to be different between genders: women in general have more fatty tissue than men and as fat contains fewer blood vessels, it doesn't play an important role in the distribution of CM. However, we corrected for the difference in proportions of men in the four groups in the statistical analysis. Second, even though cardiac output is an important factor in CM administration, it was not taken into account in this study. Timing in portal venous CT is of lesser importance compared to arterial phase scans and all patients were hemodynamically stable. It was therefore assumed that cardiac output was within normal physiological ranges in all patients.

Conclusion

The proposed 10-to-10 rule is an easily reproducible method for achieving homogeneous enhancement of the liver in portal venous abdominal CT, irrespective of patient TBW or tube voltage.

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CHAPTER 4

Finding the optimal tube current and iterative reconstruction strength in liver imaging; two needles in one haystack

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Abstract

Objectives: The aim of the study was to find the lowest possible tube current and the optimal iterative reconstruction (IR) strength in abdominal imaging.

Material and Methods: Reconstruction software was used to insert noise, simulating as if a lower tube current was used. An abdominal phantom was used to validate the performance of the ReconCT software. Thirty abdominal CT scans performed with a standard protocol (120 kV_{ref}, 150 mAs_{ref}) scanned at 90 kV, with dedicated contrast media (CM) injection software were selected. The software was used to insert noise as if the scans were performed with 90, 80, 70 and 60 % of the full dose. Consequently, the different scans were reconstructed with Filtered back projection (FBP) and IR strength 2, 3 and 4. Objective and subjective image quality were evaluated. Based on the results, lesion detection was graded by two radiologists in consensus in another 30 scans (identical scan protocol) with various liver lesions, reconstructed with IR 3, 4 and 5.

Results: A tube current of 60% still led to sufficient objective image quality when IR strength 3 or 4 were used. IR strength 4 was preferred for lesion detection. The subjective image quality was rated highest for the scans performed at 90% with IR 4.

Conclusion: A tube current reduction of 10 - 40% is possible in case IR 4 is used, leading to the highest image quality (10%) or still sufficient image quality (40%), shown by a pairwise comparison in the same patients.

Key words

Multidetector Computed Tomography; Diagnostic Imaging; Abdomen; Radiation Dose Reduction; iterative reconstructions

Introduction

Computed tomography (CT) is used on a daily basis in abdominal imaging to detect and evaluate a variety of pathologies (1, 2). While its clinical importance and benefits are undisputed, CT uses ionizing radiation, which for radiation exposure levels may lead to an increase of the lifetime attributable cancer risk (3, 4). Radiation exposure should therefore be kept "as low as reasonably achievable" according to the ALARA principle (5). Conversely, excessive radiation dose reduction can lead to insufficient diagnostic image quality, resulting in non-diagnostic scans. From a radiation safety point of view this is the worst-case scenario as no medical benefit was gained from the radiation exposure and a retake will lead in summary to an increase of the total radiation exposure. This is indicative of the delicate balance between radiation dose and image quality.

Several dose reduction techniques are applied in daily clinical practice, such as automated tube current modulation (ATCM), automated tube voltage selection (ATVS) and iterative reconstruction (IR) techniques (6-15). ATCM and ATVS optimize radiation dose by optimizing the tube current and tube voltage during the acquisition to reach sufficient image quality for each individual patient (8, 10). IR techniques are used during reconstruction of the scans to further decrease image noise, without compromising image quality (9). Based on the same raw data IR techniques result in a decrease in image noise, by repetitive calculation steps during the reconstruction. The repetition is stopped when a predefined number of cycles is reached, or when the difference between two IR steps becomes smaller than a predefined amount (16). The achievable decrease in image noise, which is related to the IR strength, can be relinquished in favour of a radiation dose reduction (17). Previous studies have shown IR techniques to be superior to filtered back projection (FBP). Although, while Hardie et al. showed a reader preference for low to intermediate IR strengths, Choy et al. demonstrated a preference for images reconstructed with IR strength 4 or 5 (18, 19). Noise decreases with an increased IR strength, but at the same time, the texture of the noise changes, possibly negatively influencing image quality (20). Therefore, in daily clinical practice, different IR strengths are used (18, 21-23).

Comparing image quality between CT scans of different patients is challenging, because differences in patient-related factors (e.g. height, weight, liver morphology and cardiac function) affect image quality (6, 15). Ideally, if one patient could be scanned several times, a reliable search for the most optimal tube current and tube voltage could be performed. Reconstruction software allows to reconstruct multiple lower tube current scans from a single raw data set. Therefore, it provides the opportunity for pairwise comparison of identical patients without the need for repetitive scanning. This software can aid in finding the optimal reference tube current and help in further decreasing radiation exposure. Previous studies showed that using dedicated post-processing software (ReconCT) for optimization a potential dose reduction of 41 to 84 % was possible in CT angiography (CTA) of various vascular structures in head and neck without compromising diagnostic image quality (24, 25). The pairwise comparison stipulates the opportunity to evaluate in abdominal imaging whether a dose reduction still leads to sufficient image quality and lesion detection. The latter being one of the most important parameters, as an increased risk of missing lesions is an unfavourable outcome. In a previous study, signal to noise ratio (SNR) and contrast to noise ratio (CNR) values of respectively 8.8 +/- 1.8 and 5.5 +/- 2.1 led to a good to excellent subjective image quality in 93.7 % of the patients (26). Therefore, it is safely to assume that a SNR above 8.0 and a CNR above 5.0 are considered sufficient.

The aim of this study was to assess both the optimal IR strength and the lowest possible tube current in abdominal CT imaging while maintaining diagnostic image quality with the use of ReconCT software.

Materials and Methods

Ethical considerations

This study was provided a waiver of written informed consent by the local ethical committee and institutional review board as retrospective data were analysed anonymously (ref METC 2017-0250).

Study design

ReconCT software (version 13.0.0.1, prototype software, Siemens Healthineers, Forchheim, Germany) was used to reconstruct raw image data at lower tube currents and different IR strengths to simulate radiation dose reduction and accompanying image quality, i.e. an increase in noise. The raw CT image data were exported directly from the CT-scanner. All scans were performed on a 3th generation dual-source CT (DSCT) scanner (Somatom Force, Siemens Healthineers, Forchheim, Germany). Validation of the software has been published elsewhere (24, 25). Although, a quality assurance has been performed in a phantom study (see Appendix).

Thirty abdominal scans were retrospectively selected and reconstructed multiple times with lower mAs percentages and IR strengths. Both objective and subjective image quality were evaluated. In addition, 30 abdominal scans all containing a diversity of liver lesions, were retrospectively selected to determine the optimal IR strength for lesion detection based on the results of the previous steps.

Patient study

Thirty abdominal scans of unique patients in portal venous phase were included between September 2019 and February 2020. Inclusion criteria were scans in which ATCM (CareDose 4D; Siemens) and ATVS (CARE kV; Siemens) techniques were used, with a reference tube voltage and tube current of respectively 120 kV_{ref} and 150 mAs_{ref}, with a slice collimation of 192 x 0.6 mm and gantry rotation time 0.5 seconds. Only scans acquired at 90 kV in which a dosing factor of 0.4 g I/kg contrast media (CM) was used, were included to ensure a homogeneous database. Dedicated CM injection software was used (P3T; Bayer Healthcare, Berlin, Germany), which calculates CM volume and flow rate, based on the linear relationship between body weight and injection duration (15). A history of liver disease or surgery was not a reason for exclusion. General exclusion criteria for a contrast-enhanced abdominal CT were applied (e.g. pregnancy, renal insufficiency [estimated glomerular filtration rate < 30 mL/min per 1.73 m^2] and iodine allergy).

The raw data of the selected scans were transferred to the ReconCT workstation, where the scans reconstructed with lower tube currents were simulated. As ATCM and ATVS techniques were used, the mAs_{eff} differed between patients, this mAs_{eff} will hereinafter be referred to as the initial value. Data were reconstructed with tube current of 90 %, 80 %, 70 % and 60 % of the initial value. Based on the phantom study, reconstructions with a tube current below 60 % were expected to be of insufficient image quality, and therefore, these data were not simulated. In addition, all scans were reconstructed with FBP and IR strengths 2, 3 and 4 (Advanced Modeled Iterative Reconstruction [ADMIRE], Siemens Healthineers, Forchheim, Germany), kernel Br40. This resulted in a total of 510 CT series (17 reconstructions for each patient).

Patients' weight was asked prior to the CT scan and together with patient' sex, age and radiation dose information (e.g. mean effective mAs [mAs_{eff}], CT dose index [$CTDI_{vol}$, in mGy] and dose length product [DLP, in mGy*m]) collected from the PACS workstation (IMPAX version 6.6.1.5003, AGFA HealthCare N.V., Mortsel, Belgium). The CM volume (in ml), total iodine load (TIL, g I), flow rate and iodine delivery rate (IDR, in g I/s) were monitored with a dedicated data acquisition program (Certega™ Informatics Solution; Bayer).

Image analysis

Data were transferred to the radiology workstation (SyngoVia™, VB30; Siemens Healthineers, Erlangen, Germany). In all reconstructions the mean Hounsfield Units (HU) and standard deviation (SD) were measured by placing the largest possible region of interest (ROI) in three different liver segments (area ≥ 1 cm^2), preferably segments 2, 5 and 8 (according to the Couinaud distribution), not containing vessels, biliary ducts or regional anomalies (e.g. cysts, metastasis or changes related to surgery) (27). The signal to noise ratio (SNR) was calculated by dividing the mean HU of the liver by its SD. The difference between the mean liver HU and the attenuation of the left paraspinal muscle, divided by the SD of the paraspinal muscle resulted in the contrast to noise ratio (CNR).

Subjective image quality

Two radiologists (B.M. and C.M.) with respectively 4- and 9-years' experience in abdominal imaging rated all scans in consensus on diagnostic screens, while being blinded to the simulated tube current and reconstruction method used. The radiologists were allowed to adjust window levels. The overall image quality and lesion detection capability were separately rated on a 5-point Likert scale (1 very poor, 2 = poor, 3 = moderate, 4 = good, 5 = excellent) (15, 28). In search for optimal image quality, scans rated as "good" or "excellent" were considered of sufficient image quality. The simulated scans with the highest percentage of scans with good or excellent image quality, were rated best.

Liver lesions

In addition to the previous patient study, 30 abdominal scans containing a diversity of liver lesions (e.g. non-specific, benign or malignant) were collected between June and August 2020. Scans were used for the evaluation of lesion detection as the presence of actual lesions, makes it easier and more reliable to evaluate this parameter. Scans were eligible for inclusion when the same scan and CM injection protocol as in the patient study was used. IR strength 3, 4 and 5 were reconstructed on the scanner, based on the results of the first patient study. Two radiologists (B.M. and C.M.) evaluated in consensus which IR strength resulted in the best liver lesions detectability. The readers had to choose the preferred strength out of the three reconstructed IR strengths. The IR strength rated most often as best for lesion detection, was declared the favoured strength.

Statistical analysis

Summaries of categorical variables were expressed as absolute numbers with percentages and continuous variables as mean ± SD. A linear mixed-effects model was used to account for the fact that of each patient 17 reconstructions are made and hence, data were correlated. The effective mAs was added to the model as covariate, with HU as dependent variable. The generalized mixed-effects model with binomial link function was used to investigate if there was an association between the IR strength and the dichotomized subjective

image quality (diagnostic image quality and lesion detection). Results of the generalized linear mixed-effects model were expressed as odds ratio (OR) and 95% confidence interval (CI). Statistical software (SPSS, version 26.0; IBM Corp, New York, NY) was used for the data analysis.

Results

Table 1. Baseline characteristics.

Parameters (N	**N = 29**
Age (years)	64.9 ± 14.2
Sex (% male)	18 (62.1 %)
Body weight (kg)	72.2 ± 9.9
Height (m)	1.73 ± 0.1
BMI (kg/m^{-2})	24.2 ± 2.4

BMI indicates body mass.

Patient study

Baseline characteristics of the population are depicted in table 1. Mean mAs_{eff}, $CTDI_{vol}$, DLP, CM volume, TIL, flow rate and IDR are shown in table 2. Data from one patient was excluded, as a higher dosing factor (in g I/kg) was used.

Table 2. Radiation dose and injection parameters.

Parameters	**N = 29**
Mean mAs_{eff}	212.0 ± 27.9
$CTDI_{vol}$ (mGy)	6.1 ± 0.8
DLP (mGy*cm)	291.4 ± 43.8
CM volume (ml)	95.8 ± 13.1
TIL (g)	28.8 ± 3.9
Flow rate (ml/s)	2.9 ± 0.6
IDR (g I/s)	0.96 ± 0.1
Dosing factor (g I/kg)	0.4

mAs_{eff} indicates effective tube current; $CTDI_{vol}$, CT dose $index_{vol}$; DLP, dose length product; CM, contrast media; TIL, total iodine load; IDR, iodine delivery rate.

To find the optimal tube current and IR strength, SNR and CNR were evaluated (figure 1). Figure 1a and 1b show in green which percentage in mAs reduction still leads to a sufficient SNR and CNR. In case IR strength 3 or 4 is used, a mAs of 60 % still results in sufficient SNR and CNR. Figure 1c depicts the overall image quality with each reconstruction strength. The odds that IR strength 3 results in a diagnostic scan was eight times higher than that of FBP

Figure 1. A signal to noise ratio (SNR) of 8.0 (A) and contrast to noise ratio (CNR) of 5.0 (B) were considered sufficient. A and B show the corresponding SNR and CNR for each combination of iterative reconstruction (IR) strength and percentage of the initial value of the tube current. In green the combination leading to sufficient objective image quality. In part C and D, the odds ratios of the overall diagnostic image quality (C) and the lesion detection capability (D) are set out. Filtered back projection (FBP) and IR strengths on the left are compared to the reconstruction methods on the x-axis. For example, the odds that IR 4 results in a better lesion detection than IR 3 is 1.2, with a confidence interval (CI) of 0.4-3.7.

A

	100%	90%	80%	70%	60%	
FBP		6.9 ± 1.5	6.5 ± 1.5	6.2 ± 1.5	5.7 ± 1.3	
IR2	8.8 ± 1.8	9.0 ± 2.0	8.5 ± 1.9	7.8 ± 2.2	7.3 ± 1.7	SNR
IR3		10.5 ± 2.3	9.6 ± 2.6	9.3 ± 2.3	8.5 ± 2.0	
IR4		12.7 ± 2.9	11.9 ± 2.8	11.2 ± 2.8	10.4 ± 2.3	

B

	100%	90%	80%	70%	60%	
FBP		4.4 ± 2.1	3.9 ± 1.8	3.6 ± 1.4	3.5 ± 1.7	
IR2	5.1 ± 2.7	5.3 ± 2.6	5.0 ± 2.3	4.7 ± 2.3	4.6 ± 2.7	CNR
IR3		6.2 ± 2.8	5.8 ± 2.4	5.3 ± 2.6	5.1 ± 2.5	
IR4		7.3 ± 3.4	7.1 ± 3.6	6.7 ± 3.5	6.2 ± 3.2	

C

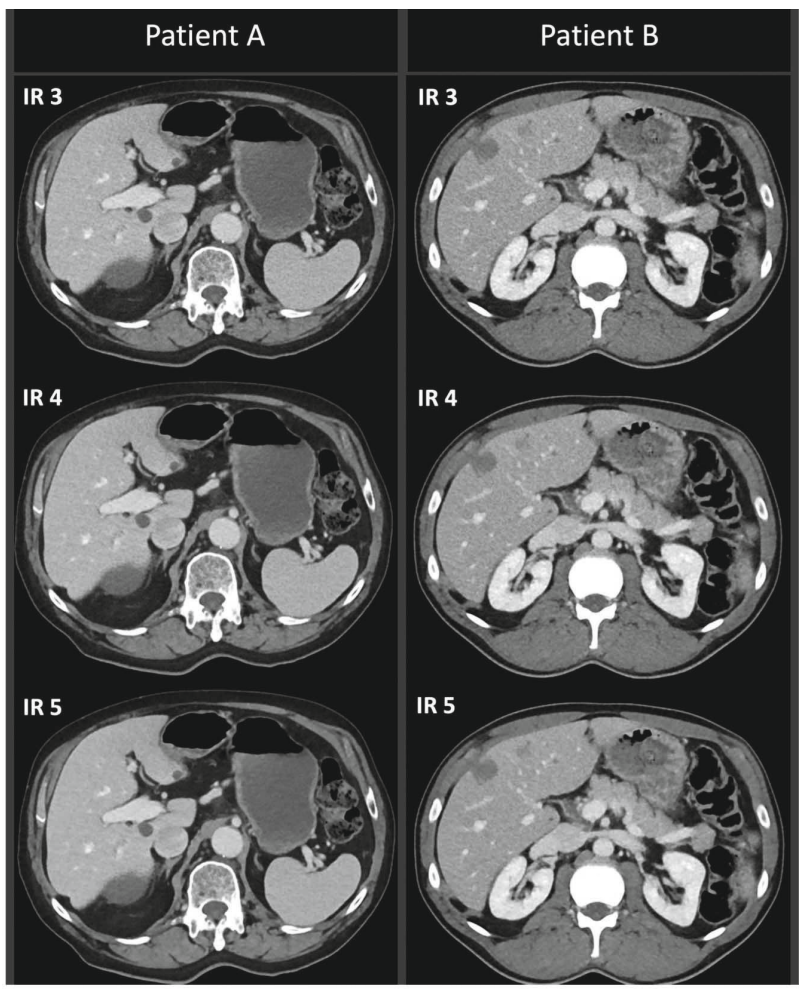
	Compared with				
	FBP	IR2	IR3	IR4	
FBP		0.3 (0.1-0.8)	0.1 (0.0-0.5)	0.3 (0.1-0.8)	*Diagnostic Image*
IR2	3.7 (1.2-11.1)		0.5 (0.1-1.9)	1.0 (0.3-3.6)	*Quality*
IR3	8.0 (2.1-30.3)	2.1 (0.5-8.9)		2.2 (0.5-9.3)	*Odds ratio (CI 95%)*
IR4	3.6 (1.2-11.2)	1.0 (0.3-3.5)	0.5 (0.1-1.9)		

D

	Compared with				
	FBP	IR2	IR3	IR4	
FBP		0.2 (0.1-0.5)	0.2 (0.1-0.4)	0.1 (0.0-0.4)	
IR2	5.6 (2.2-14.3)		0.9 (0.3-2.6)	0.8 (0.3-2.2)	*Lesion Detection*
IR3	6.4 (2.4-17.0)	1.1 (0.4-3.3)		0.8 (0.3-2.6)	*Odds ratio (CI 95%)*
IR4	7.5 (2.7-20.7)	1.3 (0.4-4.0)	1.2 (0.4-3.7)		

and more than two times higher than strength 2 and 4. The odds that IR 4 results in a better lesion detection was 7.5 times higher than that of FBP and respectively 1.3 and 1.2 times higher than that of IR 2 and IR 3 (figure 1d).

Figure 2. Abdominal scan of an 86-year-old patient (Patient A) in the follow-up for a urothelial cell carcinoma, who has multiple cysts in the liver parenchyma. In addition, a scan of a 47-year-old male (Patient B) in the follow-up for hepatic metastasis of colorectal cancer. Both scans are reconstructed with IR strength 3, 4 and 5. The scans reconstructed with IR 4 were rated in consensus to have the best lesion detection capability



A mAs of 60 % with the use of IR strength 3 or 4, still leads to sufficient objective image quality. The overall subjective diagnostic image quality was highest for IR 3. IR 4 was graded best for lesion detection.

The percentage of scans considered of sufficient diagnostic image quality (rated as of good or excellent diagnostic image quality) was highest (89.7 %) for the scan at 100 % with IR 2. With IR 3 at 90, 80, 70 and 60 % respectively 79.3, 69.0, 65.5 and 48.3 % of the scans was rated sufficient. Sufficient diagnostic image quality was reached in 82.8, 72.4, 79.3 and 55.2 %, respectively at IR 4. Regarding lesion detection, the percentage of sufficient scans was 79.3 % at 100 % with IR 2, while at IR 3 the percentages at 90, 80, 70 and 60 % were respectively 72.4, 62.1, 55.2 and 37.9 %. At IR 4 the percentage of scans rated as excellent or good was 86.2, 69.0, 69.0 and 55.2 % respectively.

Liver lesions

This second patient population confirmed the preference for IR strength 4 regarding lesions detection. In twenty-five cases IR strength 4 was most appreciated, while IR 3 was valued highest in 4 cases and IR 5 in only one case. Examples of two cases in which IR 4 was preferred are depicted in figure 2.

Discussion

The aim of the study was to find the optimal IR strength and the lowest possible (reference) tube current that could be used in abdominal CT imaging, without compromising objective and subjective image quality. In accordance with the literature, IR techniques outperformed FBP (18, 19, 22). When IR techniques are used, the mAs_{ref} can be reduced without compromising objective image quality. The results indicate that with IR strength 3 or 4, reductions of up to 40 % still produce a sufficient SNR and CNR. Scans performed with IR 4 at 90 % tube current, led to a slightly higher lesion detection capability compared to the full dose at IR strength 2. Therefore, it can be concluded that the mAs_{ref} in abdominal imaging can be safely reduced by 10 – 40 %, in case IR strength 4 is used on this particular scanner, showed by pairwise comparison. Ten percent reduction at IR 4 leads to the highest image quality, while a reduction of 40 % at IR strength 4 still results in sufficient image quality.

For the first patient study, only scans with IR strength 2 to 4 were reconstructed. IR strength 1 and 5 were not reconstructed. From experience, IR 1 was expected to result in very noisy images and IR 5 in images appearing very smoothened. IR 4 turned out to result in subjectively the best lesion detection capability. Subsequently, the second study was performed, in which IR 5 was incorporated in addition to IR strength 3 and 4 to rule out possible superiority of IR strength 5.

A number of studies have evaluated the possibility to reduce radiation dose in abdominal imaging (23, 29-33). To the best of our knowledge, this is the first study comparing different radiation doses and IR strengths in abdominal imaging, within the same patient by using reconstruction software. The study set up can be used to investigate the optimal tube current and IR algorithm for each anatomical region, scan indication, vendor and specific scanner.

Our study evaluated both objective and subjective image quality. For the latter, as the name already implies, it is subjective and some readers might prefer more noise for a particular scan indication, while others prefer smoothened scans (17). Establishing the objective image quality with SNR and CNR seems rather straightforward. Although, when searching for reliable thresholds, a wide

variety of values is found in the literature, all presumed to be of diagnostic image quality, and no clear cut off values are established (33-37). In addition, previous literature states that both SNR and CNR might not encompass the complete appreciation of image quality (38, 39). The present study sets out the discrepancy between objective and subjective image quality. According to the SNR and CNR values a radiation dose reduction of 40 % was possible, while looking at the subjective parameters only a smaller tube current reduction of 10 - 40 % seemed feasible. This indicates the struggle to be able to safely declare that CT scans are of sufficient image quality. Future research could focus on determining new, more universal objective parameters to reliable, generalizable and consequently assess image quality. Such parameters would make it possible to establish with a higher degree of certainty if image quality is diagnostic and if all the different developed radiation dose reduction algorithms and reconstructions results in sufficient image quality for diagnostic purposes.

Limitations

The study is a single-center study with a rather small patient sample. In addition, the golden standard for lesion detection and characterization is autopsy, which was not performed. The baseline protocol for abdominal imaging chosen in present study was the scan and CM injection protocol as used in daily clinical practice. This assumes that this baseline scan protocol is considered to be of good – maybe even too good - image quality, while this protocol might potentially have benefitted from a (small) increase in dose. Lastly, radiation dose reduction and IR strengths were only studied on a CT scanner from one vendor, which limits generalizability of the outcome. As the software is vendor specific and raw data based it is therefore not applicable to scanners form other vendors.

Conclusion

IR strength 4 leads to the best subjective image quality in abdominal CT imaging and gives the opportunity to reduce the tube current by 10 to 40 % without compromising both objective as well as subjective image quality as shown by pairwise comparison in the same patients with the use of ReconCT software.

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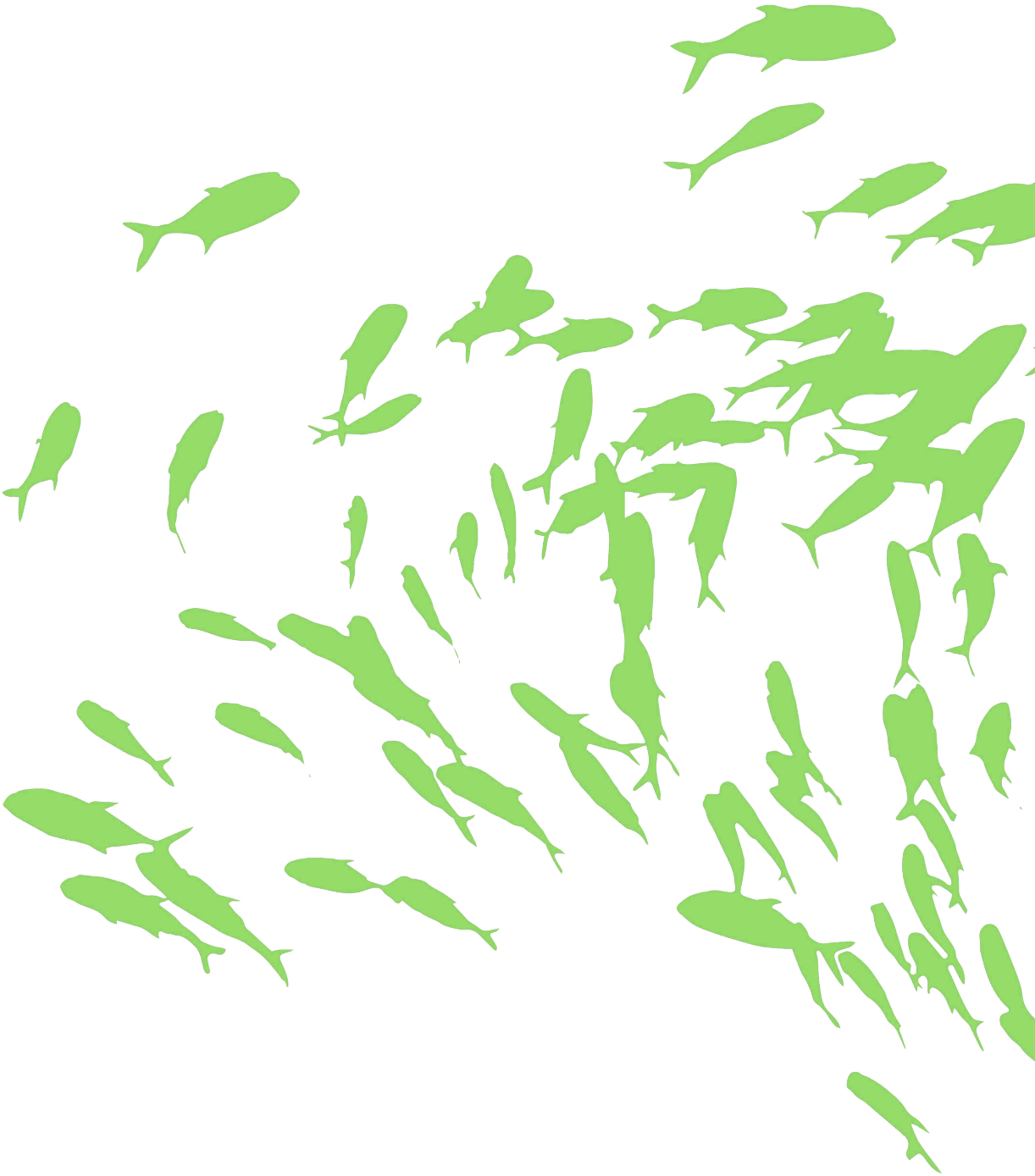

CHAPTER 5

Individualized scan protocols in abdominal computed tomography: radiation versus contrast media dose optimization

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Abstract

Background: In contrast-enhanced abdominal computed tomography (CT), radiation and contrast media (CM) injection protocols are closely linked to each other and therefore a combination is the basis for achieving optimal image quality. However, most studies focus on optimizing one or the other parameter separately.

Purpose: Reducing radiation dose may be most important for a young patient or a population in need of repetitive scanning, whereas CM reduction might be key in a population with insufficient renal function. The recently introduced technical solution, in the form of an automated tube voltage selection slider [ATVS], might be helpful in this respect. The aim of the current study was to systematically evaluate feasibility of optimizing either radiation or CM dose in abdominal imaging compared to a combined approach.

Methods: Six Göttingen minipigs (mean weight 38.9 ± 4.8 kg) were scanned on a 3rd-generation dual source CT. ATVS and automated tube current modulation (ATCM) techniques were used, with quality reference values of 120 kV_{ref} and 210 mAs_{ref}. ATVS was set at 90 kV semimode. Three different abdominal scan and CM protocols were compared intra-individually: 1. the standard "combined" protocol, with the ATVS slider position set at 7 and a body weight adapted CM injection protocol of 350 mg I/kg body weight, iodine delivery rate (IDR) of 1.1 g I/s; 2. the CM dose saving protocol, with the ATVS slider set at 3 and CM dose lowered to 294 mg I/kg, resulting in a lower IDR of 0.9 g I/s; 3. the radiation dose saving protocol, with the ATVS slider position set at 11 and a CM dose of 441 mg I/kg and an IDR 1.3 g I/s, respectively. Scans were performed with each protocol in arterial, portal venous and delayed phase. Objective image quality was evaluated by measuring the attenuation in Hounsfield Units (HU), signal-to-noise ratio (SNR), and contrast-to-noise ratio (CNR) of the liver parenchyma. The overall image quality, contrast quality, noise and lesion detection capability were rated on a 5-point Likert scale (1 = excellent, 5 = very poor). Protocols were compared for objective image quality parameters using one-way ANOVA, and for subjective image quality parameters using Friedman test.

Results: Mean radiation doses were 5.2 ± 1.7 mGy for the standard protocol, 7.1 ± 2.0 mGy for the CM dose saving protocol, and 3.8 ± 0.4 mGy for the radiation dose saving protocol. Mean total iodine load (TIL) in these groups was 13.7 ± 1.7, 11.4 ± 1.4 and 17.2 ± 2.1 g, respectively. No significant differences in subjective overall image or contrast quality were found. SNR and CNR were not significantly different between protocols in any scan phase. Significantly more noise was seen when using the radiation dose saving protocol ($P < 0.01$). In portal venous and delayed phases, mean attenuation of the liver parenchyma significantly differed between protocols ($P < 0.001$). Lesion detection was significantly better in portal venous phase using the CM dose saving protocol compared to the radiation dose saving protocol ($P = 0.037$).

Conclusion: In this experimental set-up, optimizing either radiation (-26 %) or CM dose (-16 %) is feasible in abdominal CT imaging. Individualizing either radiation or CM dose leads to comparable objective and subjective image quality. Personalized abdominal CT examination protocols can thus be tailored to individual risk assessment and might offer additional degrees of freedom.

Key words

Computed tomography; abdomen; liver; contrast media; radiation dose; renal insufficiency; age; image quality; automated tube voltage selection

Introduction

Computed tomography (CT) of the abdomen is the workhorse of daily clinical practice and is used for the diagnosis of a wide variety of pathologies (1). In recent years, contrast media (CM) injection protocols have been individualized based on different body size parameters (e.g. total body weight, body surface area, and lean body weight) (2-10). Similarly, modern CT scanners automatically individualize both tube current (automated tube current modulation; ATCM) and tube voltage (automated tube voltage selection; ATVS) based on patient body habitus. ATVS techniques are intended for contrast-enhanced CT scans, because they exploit the strong increase of iodine attenuation at lower tube voltage. Depending on patient body shape and imaging task, ATVS proposes the tube voltage that provides a desired contrast-to-noise ratio (CNR) at lowest radiation dose (11-13) – typically the lowest tube voltage with sufficient tube current reserves for the planned examination. The extent of radiation dose reduction at lower kV can be controlled by the user, e. g. by applying different slider settings. In its vendor-recommended parametrization, ATVS focuses on radiation dose reduction and assumes the same CM protocol is used at all tube voltages. CNR, however, is a combination of both radiation dose and iodine contrast. Therefore, by decreasing radiation dose beyond the proposed ATVS parameters (e. g. by deviating from the vendor-recommended slider settings), and at the same time increasing CM dose (or vice versa), similar CNR's can be reached (5). This offers perspective for further individualization of radiation and CM protocols. For example, in younger patients and/or in patients requiring repetitive scanning, a protocol favoring radiation dose reduction is preferred over a decrease in CM dose, so as to minimize the increase in lifetime attributable cancer risk due to ionizing radiation exposure (14-16). On the other hand, in the elderly where reduced renal function is more common, a decrease in CM dose is preferred over radiation dose reduction (17). Both radiation dose and CM injection protocols can be manually adapted, but the slider bar provided in ATVS to tailor the scan protocol offers a user-friendly alternative.

The current study aims to evaluate the feasibility of using standard ATVS slider positions combined with adapted CM injection protocols for reducing either radiation or CM dose, depending on individual risk assessment, compared to a standard combined protocol. This was done by structurally comparing

objective and subjective image quality parameters in imaging of the abdomen within and between subjects.

Materials and Methods

Animals

The study was performed on 6 healthy female Göttingen minipigs (Ellegaard, Dalmose, Denmark) with a mean body weight of 38.9 ± 4.8 kg. Three imaging protocols were compared intra-individually in all 6 animals with at least one week between examinations.

The animals were handled in compliance with the German Animal Welfare Legislation and approval of the State Animal Welfare Committee. All measurements were performed under general anesthesia and animals were orally intubated and mechanically ventilated. Animals were placed in a prone position and CT imaging was performed during end-expiratory ventilation stop.

Study design

CT imaging was performed on a third-generation dual source CT scanner (Somatom Force, Siemens Healthineers, Forchheim, Germany). Abdominal scans were done using slice collimation 192 × 0.6 mm, rotation time 0.5 s and pitch 0.85, resulting in a scan time of 4 s. Image reconstruction was done with a Br40 kernel, SAFIRE iterative reconstruction (level 3) at 0.75 mm slice thickness with 0.5 mm increment. The ATVS system (CAREkV, Siemens Healthineers) was operated with 90 kV semimode, ATCM and fixed quality reference values (120 kV, 210 mAs). The ATVS slider position is determined by the scan indication. For parenchymal (e. g. liver) studies, the vendor recommends position 7 to balance image noise increase and increased CM attenuation at lower tube voltage. The standard protocol in this study was performed with this configuration (slider position 7). At lower slider settings, less image noise increase is accepted at lower tube voltage, with the consequence of higher radiation dose. Level 3, originally intended for non-contrast scans, can therefore be used to perform CT scans with similar CNR compared to level 7 but reduced CM volume. This is the CM dose saving protocol used in present study. At slider position 11 -

originally intended for CT angiographic examinations - more image noise is accepted at further reduced radiation dose. To maintain the expected CNR of slider level 7, the CM volume needs to be increased. This is the radiation dose saving protocol. The protocol specific CT scan configurations were combined with adapted CM injection protocols. Iopromide (Ultravist 300, Bayer AG, Berlin, Germany) was used and CM administration was performed with the Medrad Centargo CT injection system (Bayer AG) into the ear vein of the animals. For the standard imaging protocol 350 mg I/kg body weight was administered with a flow rate of 3.5 ml/s, the Iodine delivery rate (IDR) was 1.1 g I/s. For the CM dose saving protocol, the used standard dose (350 mgI/kg) was reduced by 16 % to 294 mg I/kg and flow rate was adapted to 2.9 ml/s (IDR 0.9 g I/s), so as to maintain the same total injection time. A 26 % higher CM dose (441 mgI/kg) than the used standard dose administered at 4.4 ml/s (IDR 1.3 g I/s) was used for the low radiation dose protocol (18). All CM injections were followed by a 20 ml saline chaser applied at the same flow rate. A summary of the combination of the scanner configuration and CM injections for each imaging protocol is given in table 1.

Contrast timing was adjusted with bolus tracking in the descending aorta using a threshold of 100 HU. Arterial phase imaging started with a delay of 5 s followed by the portal-venous and late phase using fixed delays of 60 s and 90 s.

The CTDI radiation doses were obtained from the dose reports of the CT scanner. The percentage change in relation to the standard imaging protocol was calculated.

Objective image quality

The data was evaluated on post-processing software (SyngoVia™, VB30; Siemens Healthineers, Erlangen, Germany). The Hounsfield Unit (HU) and standard deviation (SD) were measured in the hepatic artery in arterial phase, by placing a region of interest (ROI) as large as possible in the vascular structures, taking into account the vasculature wall. In portal venous phase, three ROI's (area ≥ 2 cm^2) were drawn in three different liver segments. Preferably in segment 2, 5 and 8, according to the Couinaud distribution, not containing vessels or biliary

ducts (19). Another as large as possible ROI was placed in the portal vein to measure the signal attenuation. The SD of the paraspinal muscle (ROI area ≥ 1 cm^2) was used to estimate image noise. The signal-to-noise ratio (SNR) was calculated by dividing the mean HU of the three liver segments by the noise. The attenuation of the left paraspinal muscle was used to calculate the CNR. Mean liver HU minus the HU of the paraspinal muscle, divided by the SD of the paraspinal muscle resulted in the CNR. Similar calculations were performed for the delayed phase.

Subjective image quality

The scans were rated in consensus on diagnostic screens by two radiologists (C.M. and B.M.) with 10- and 5-years' experience in abdominal imaging. Adjusting the window level was allowed. The overall image quality, noise and contrast quality were rated on a 5-point Likert scale (1 = excellent, 2 = good, 3 = moderate, 4 = poor, 5 = very poor) (7, 20). Lesion detection was rated in portal venous and delayed phase using the same Likert scale. The arterial phase is not solely used for liver lesion detection at our center, therefore this parameter was not considered relevant.

Statistics

All results are presented as mean ± SD, or median with interquartile range (IQR) for subjective image quality. Heart rate, attenuation, SNR and CNR were compared between the three imaging protocols using one-way analysis of variance on ranks (ANOVA) followed by the post-hoc Tukey's multiple comparisons test. Subjective image quality parameters were compared between protocols using the Friedmann test followed by the Dunn's test for multiple comparison. Two-sided P values < 0.05 were regarded as statistically significant. Statistical analyses were performed using GraphPad Prism (GraphPad Software version 8, La Jolla, CA, USA).

Results

Injection parameters and radiation dose

Mean heart rates did not significantly differ between protocols: 104 ± 20 bpm (standard), 105 ± 11 bpm (CM saving) and 102 ± 24 bpm (radiation saving). Table 1 shows an overview of radiation dose and CM injection parameters. As a result of the study design, CM volumes and radiation doses differed between groups. In the standard protocol, the $CTDI_{vol}$, mean CM

Table 1. Contrast media (CM) and radiation dose parameters

		Protocol	
	Standard (n = 6)	CM dose saving (n = 6)	Radiation dose saving (n = 6)
Radiation dose parameters			
CAREkV	90 kV semimode	90 kV semimode	90 kV semimode
Reference (kV/mAs)	120 / 210	120 / 210	120 / 210
Slider position	7	3	11
$CTDI_{vol}$ (mGy)	5.2 ± 1.7	7.1 ± 2.0	3.8 ± 0.4
CM injection parameters			
Concentration (mg I/ml)	iopromide 300	iopromide 300	iopromide 300
CM dose (mg I/kg)	350	294	441
Mean CM volume (ml)	45.5 ± 5.5	38 ± 4.8	57.3 ± 6.9
TIL (g)	13.7 ± 1.7	11.4 ± 1.4	17.2 ± 2.1
Flow rate (ml/s)	3.5	2.9	4.4
IDR (g I/s)	1.1	0.9	1.3
Saline chaser (ml)	20	20	20

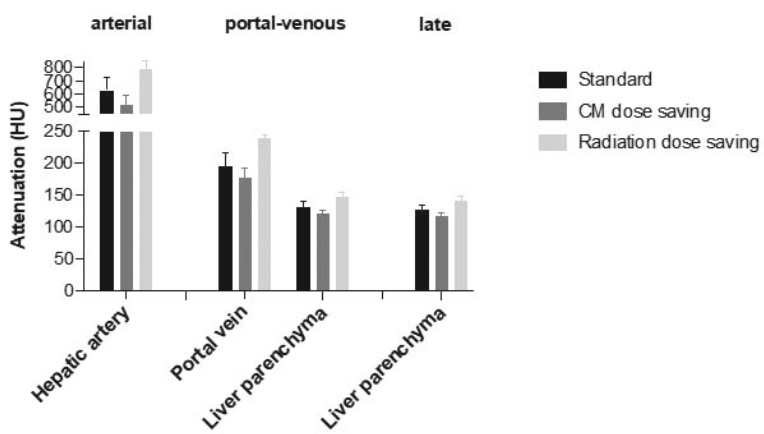
TIL, total iodine load; IDR, iodine delivery rate (in g I/s); $CTDI_{vol}$, CT dose index vol;

volume, and TIL were 5.2 ± 1.7 mGy, 45.5 ± 5.5 ml and 13.7 ± 1.7 g, respectively. The mean radiation dose was higher in the CM dose saving group and lower in the radiation dose saving group, with values of 7.1 ± 2.0 and 3.8 ± 0.4 mGy respectively. The TIL was lowest in the CM dose saving group (11.4 ± 1.4 g) and highest for the radiation dose saving group (17.2 ± 2.1 g).

Objective image quality

Significant differences in attenuation (HU) of the hepatic artery in arterial phase, and attenuation of the portal vein and liver in portal venous and the liver in delayed phase were found, with P values < 0.001 in all cases (figure 1). Mean attenuation of the liver parenchyma in portal venous phase was 130.6 ± 10.5 HU for the standard protocol. Attenuation was lower using the CM dose saving protocol (121.3 ± 4.9 HU) and higher using the radiation dose saving protocol (148.3 ± 6.3 HU) (P < 0.001).

Figure 1. Effect of contrast media (CM) and radiation dose protocols on mean attenuation of the hepatic artery, portal vein and liver parenchyma in three different scan phases. Error bars indicate the standard deviation.



Abbreviations: HU: Hounsfield units

SNR and CNR did not significantly differ between groups in the arterial, portal venous, or delayed phases (figure 2). Mean SNR of the liver in portal venous phase was 8.2 ± 1.1 for the standard protocol, 9.8 ± 1.7 for the CM dose saving protocol, and 8.6 ± 0.5 for radiation dose saving protocol (P= 0.188). Mean CNR for the three protocols was 4.5 ± 1.3, 4.5 ± 1.0 and 4.5 ± 0.4, respectively (P = 0.990) (table 2).

Figure 2. Effect of contrast media (CM) and radiation dose protocols on signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) of the hepatic artery, portal vein and liver parenchyma in three different scan phases. Error bars indicate the standard deviation.

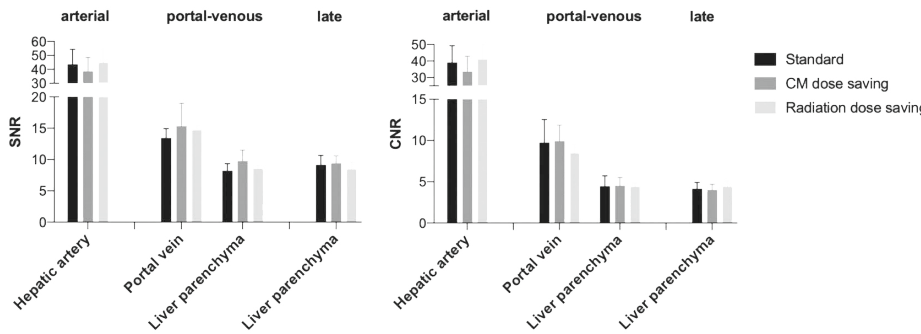


Table 2. Objective and Subjective image quality parameters

	Protocol			
	Standard	**CM dose saving**	**Radiation dose saving**	**P**
Arterial phase				
Objective image quality				
Mean HU hepatic artery	627.5 ± 99.6	518.3 ± 75.2	788.5 ± 59.4	< 0.001[1]
Mean HU liver parenchyma	81.4 ± 11.2	81.6 ± 15.0	97.5 ± 25.3	0.267
SNR Liver	5.6 ± 1.0	6.0 ± 1.5	5.6 ± 1.8	0.838
CNR Liver	1.1 ± 1.0	1.3 ± 1.1	1.8 ± 1.5	0.66
Subjective image quality (median, IQR)				
Overall	3 (2-3)	2.5 (2-3)	3 (3-3.3)	0.259
Noise	3 (2.8-3.3)	2.5 (2-3)	4 (3.8-4)	0.004[2]
Contrast	2 (1.8-2.3)	2 (1.8-2)	2 (1-2)	0.889
Portal venous phase				
Objective image quality				
Mean HU portal vein	195.3 ± 21.9	177.7 ± 15.8	239.3 ± 4.9	< 0.001[3]
Mean HU liver parenchyma	130.6 ± 10.5	121.3 ± 4.9	148.3 ± 6.3	< 0.001[4]
SNR Liver	8.2 ± 1.1	9.8 ± 1.7	8.6 ± 0.5	0.118
CNR Liver	4.5 ± 1.3	4.5 ± 1.0	4.5 ± 0.4	0.990
Subjective image quality (median, IQR)				
Overall	2 (1.8-3)	1.5 (1-2)	2 (2-2.3)	0.049[6]
Noise	2.5 (2-3)	2 (1-2)	3 (3-3.3)	0.001[2]
Contrast	2 (1.8-2)	1.5 (1-2)	2 (2-2)	0.222
Lesion detection	1.5 (1-2.3)	1 (1-1.3)	2 (2-2)	0.037[2]

Table 2. Continued

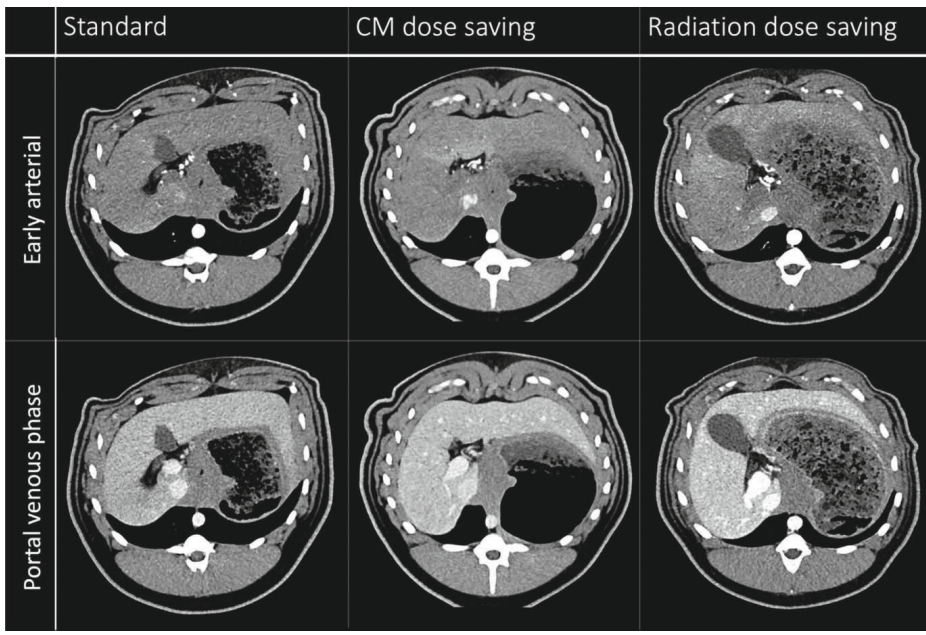
	Protocol			
	Standard	**CM dose saving**	**Radiation dose saving**	**P**
Delayed phase				
Objective image quality				
Mean HU liver parenchyma	127.1 ± 7.7	117.1 ± 5.4	142.4 ± 6.3	< 0.001[5]
SNR Liver	9.2 ± 1.5	9.4 ± 1.2	8.5 ± 1.0	0.504
CNR Liver	4.2 ± 0.8	4.0 ± 0.7	4.5 ± 0.6	0.592
Subjective image quality (median, IQR)				
Overall	2.5 (2-3)	2 (1.8-2)	3 (2-3)	0.086
Noise	3 (2-3)	2 (2-2.3)	4 (3.8-4)	0.002[2]
Contrast	2 (2-2)	2 (1.8-2)	2 (2-2)	> 0.99
Lesion detection	2 (2-3)	2 (1.8-2)	2 (2-3)	0.333

Mean attenuation (mean HU), signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) in different scan phases using different CM protocols and slider positions, as well as the subjective (overall) image quality. HU indicates Hounsfield Units.
[1] Post hoc comparison showed a significant difference between standard and radiation dose saving (P = 0.01) and between CM dose saving and radiation dose saving (P < 0.001)
[2] Post hoc comparison showed a significant difference between CM dose saving and radiation dose saving.
[3] Post hoc comparison showed a significant difference between standard and radiation dose saving (P = 0.002) and between CM dose saving and radiation dose saving (P < 0.001).
[4] Post hoc comparison showed a significant difference between standard and radiation dose saving (P = 0.005) and between CM dose saving and radiation dose saving (P < 0.001).
[5] Post hoc comparison showed a significant difference between standard and CM dose saving (P = 0.05), between standard and radiation dose saving (P = 0.005) and between CM dose saving and radiation dose saving (P < 0.001)
[6] Post hoc comparison showed no significant difference between groups.

Subjective image quality

Overall subjective image quality and assessment of contrast did not significantly differ between protocols (table 2). Lesion detection was significantly better in the CM dose saving protocol compared to the radiation dose saving protocol in portal venous phase (P = 0.037). The IQR for lesion detection using the standard protocol varied between good and excellent (1 - 2.3). Using the CM dose saving protocol the IQR was excellent (1 - 1.3) and using the radiation dose saving IQR was good (2 – 2). No significant differences in lesion detection were

Figure 3. Example of acquired images of repeated scans in a single subject. Three different contrast media (CM) and radiation dose protocols were used. Standard protocol: 350 mgI/kg CM, iodine delivery rate (IDR) 1.1 g I/s , slider position 7; CM dose saving protocol: 294 mgI/kg CM, IDR 0.9 g I/s, slider position 3; radiation dose saving protocol: 441 mgI/kg CM, IDR 1.3 g I/s, slider position 11.



found in delayed phase (P = 0.333). Noise was rated lowest – corresponding with a better value on the Likert scale - for the CM dose saving protocol, and significantly higher for the radiation dose saving protocol (P < 0.01) for all three phases. Figure 3 shows an example of images acquired from a single pig scanned several times in arterial and portal venous phases using the three protocols (standard, CM dose saving, and radiation dose saving).

Discussion

The results of the current study show that optimizing either the radiation or the CM dose is feasible in abdominal CT imaging by combining scan and injection protocols. Based on an individual risk assessment it seems possible to reduce either one of the parameters, without negatively influencing the objective and subjective image quality. Both SNR and CNR were comparable between groups in all scan phases (arterial, portal venous and delayed phase). The attenuation of the liver parenchyma was significantly different between groups in portal venous and delayed phases, however expected based on the study design. The tube voltage was kept constant in each group (90 kV), while the CM injection protocol differed between groups. In the radiation dose saving group TIL was highest and TIL was lowest in the CM dose saving group. The overall and contrast image quality did not significantly differ between groups. Noise was rated significantly higher in the radiation dose saving group, in all scan phases. Lesion detection was good to excellent in portal venous and delayed phase, with a significantly higher score for images acquired in portal venous phase using the CM dose saving protocol. Overall subjective image quality was higher for images acquired using the CM dose saving protocol, but post hoc comparison found no significant difference between groups.

The current study uses a more integrated approach, where previous studies on this topic have more disconnected set ups (e.g., optimizing CM dose based on patient body composition or individualizing radiation dose based on ATCM and ATVS techniques) (2-6, 21-24). The current results show that it is feasible to adapt either radiation or CM dose to individual risk assessment. As opposed to a more disconnected approach, using the ATVS slider offers an integrated concept.

By adjusting the slider settings in the semimode of the ATVS system on a third-generation dual-source CT scanner, Euler et al. showed that optimizing either radiation or CM dose led to comparable image quality in low kV CT angiography imaging, compared to a standard 120 kV exam (13). A 34.3 % reduction in radiation dose or a 20.2 % reduction in CM dose was feasible without significant difference in overall subjective image quality among protocols. In vascular imaging, in general more noise is accepted in order to be able to reliably assess

vascular structures because surrounding organs are of less importance. In parenchymal studies, the balance between noise and attenuation of the organs is much more delicate. Both excessive noise and insufficient CM attenuation might result in diagnostic insufficiency, for example an inability to detect liver lesions. Earlier studies focused on CM reduction in patients with reduced kidney function. By decreasing tube voltage, a substantial reduction in CM could be achieved without negatively influencing either objective or subjective image quality (25, 26). Reducing both parameters at the same time will decrease CNR, and may lead to insufficient image quality (13). However, in the current study CNR was comparable between groups by adapting either radiation or CM dose, as intended in the study design.

Surprisingly, although not significant, the contrast was rated highest in images acquired using the CM saving protocol for both portal venous and delayed phases. Possible explanations are twofold. First, even though intra-individual comparisons provide a unique opportunity for protocol evaluation, the small population of 6 means that each subjective image quality contributes to a sixth of the end result. Second, a combination of the factors scored in the current study (noise, contrast, and lesion detection) determine subjective image quality, and results may reflect the fact that it is difficult for readers to separate parameters (27). For example, image quality of a low noise, mediocre contrast enhancement CT image may still be evaluated 'good', because the lack in CM enhancement is masked by low noise level. Unfortunately, to date, no objective parameter exists which is able to reliably quantify image quality in a way which incorporates both objective and subjective aspects.

Image quality depends on both scan parameters (radiation dose related) and CM injection protocol (CM dose related). Radiation and CM dose can be calculated for each individual patient and the resulting data manually entered into scanner and injector devices. ATVS techniques automatically individualize radiation dose which can be very useful, but the aim is radiation dose reduction only. Information regarding the CM injection protocol (e.g., CM volume) is not taken into account despite playing a role in ATVS methodology (11-13). ATCM and ATVS together optimize radiation dose by adjusting tube current and tube voltage, based on the clinical question and patient characteristics. By incorporating the CM injection protocol into these algorithms, protocols can be

further adapted to individual requirements, such as for patients with reduced kidney function or young age, or to specific disease management regimes and active surveillance.

The current study has some limitations. First, it is a single-center animal study, and both generalization and translation to humans may be limited. However, Göttingen minipigs have been shown to be suitable as minipigs are anatomically comparable to humans (28, 29). Second, as the animals were healthy, no liver lesions could be evaluated, which makes the parameters 'lesion detectability' slightly arbitrary. Another limitation is that the ATVS slider adjustment is a vendor specific technique and results presented might therefore not directly be generalizable to other vendors.

In conclusion, in this experimental setup, optimizing either radiation (-26 %) or CM dose (-16 %) resulted in comparable objective and subjective diagnostic image quality in abdominal CT. This study demonstrates the feasibility of protocol individualization by adapting a combination of scan and CM injection parameters, which offers new opportunities for taking into account patient-related risk factors such as age and kidney function.

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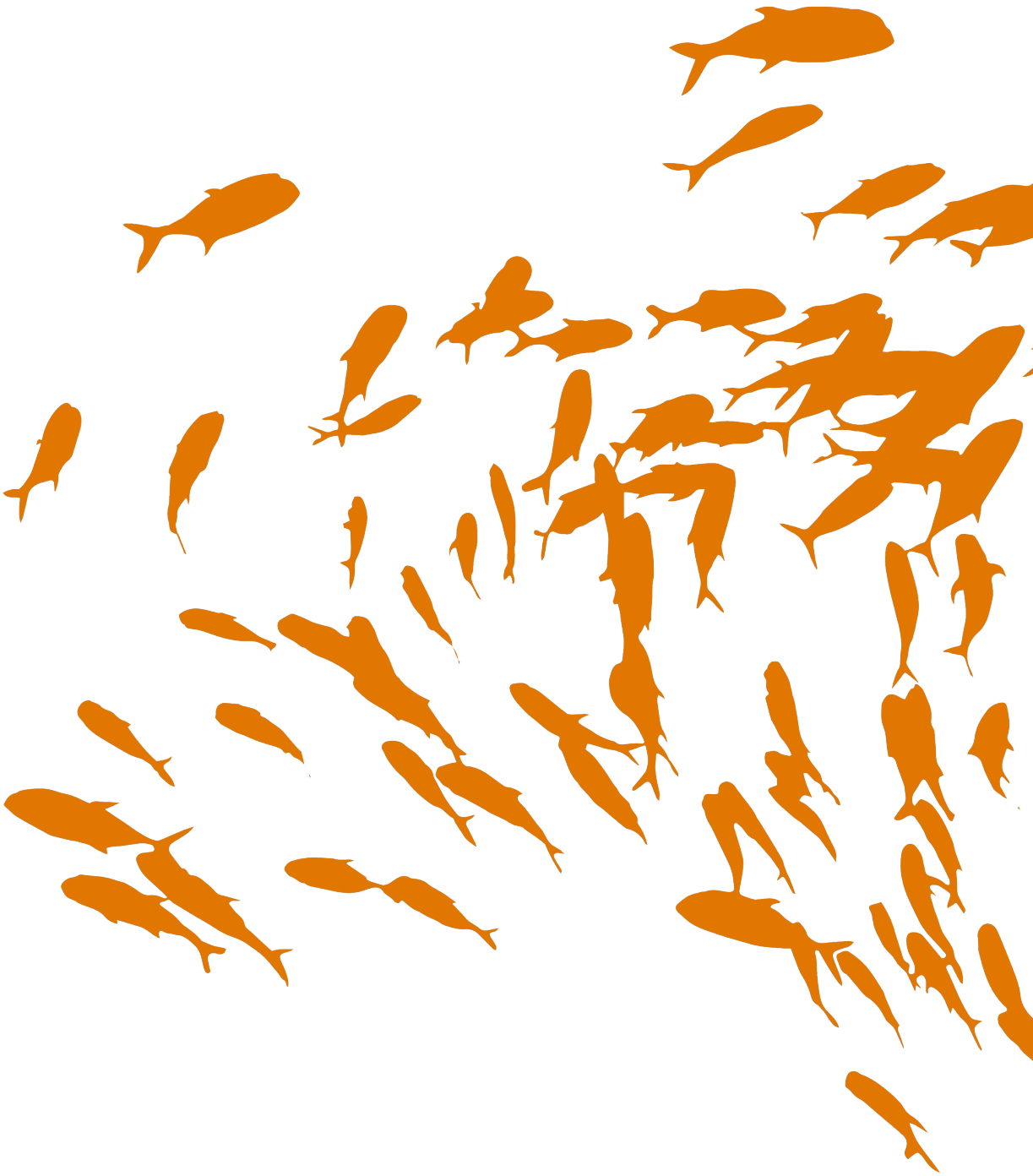

CHAPTER 6

Influence of contrast material temperature on patient comfort and image quality in computed tomography of the abdomen (CATCHY): a randomized controlled trial

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Abstract

Background: International guideline-recommendations on safe use of contrast media (CM) are conflicting regarding the necessity to pre-warm iodinated CM.

Purpose: Aim of the study was to evaluate the effects of room temperature CM compared to pre-warmed CM on image quality, safety and patient comfort in abdominal computed tomography (CT).

Methods: CATCHY is a double-blinded, randomized non-inferiority trial. Between February and August 2020, 218 participants referred for portal venous abdominal CT were prospectively and randomly assigned to one of two groups. All patients received iopromide at 300mgI/ml: group 1 at room temperature (~23°C [~73°F]), group 2 pre-warmed to body temperature (37°C [99°F]). A state-of-the-art individualized CM injection protocol was used, based on body weight and adapted to tube voltage. Primary outcome was absolute difference in mean liver attenuation between groups, calculated with a two-sided 95% confidence interval. The non-inferiority margin was set at -10HU. Secondary outcomes were objective (signal-to-noise [SNR] and contrast-to-noise ratios [CNR]) and subjective image quality; CM extravasations and other adverse events; and participant comfort (five-point scale questionnaire) and pain (numeric rating scale). This trial is registered with ClinicalTrials.gov (NCT04249479).

Results: The absolute difference in mean attenuation between groups was +4.23HU (95% CI +0.35 to +8.11; mean attenuation 122.2±13.1HU in group 1, 118.0±15.9HU in group 2; P=0.03). SNR, CNR and subjective image quality were not significantly different between groups (P=0.53, 0.23 and 0.99 respectively). Contrast extravasation occurred in one patient (group 2), no other adverse events occurred. Comfort scores were significantly higher in group 1 than in group 2 (P=0.03), pain did not significantly differ (perceived P>0.99; intensity P=0.20).

Conclusion: Not pre-warming iodinated CM was found non-inferior in abdominal CT imaging. Pre-warming conferred no beneficial effect on image quality, safety, and comfort, and might therefore no longer be considered a prerequisite in state-of-the art injection protocols for parenchymal imaging.

Key words

Multidetector Computed Tomography; Diagnostic Imaging; Abdomen; Contrast Media; Image Quality; Contrast Material Warming; Discomfort.

Introduction

Computed tomography (CT) has rapidly evolved (1-3). Both scan and contrast media (CM) protocols have been individualized based on patient characteristics as well as for clinical indications (4-8). The effects of various characteristics of CM have been thoroughly investigated (8-16). Among these, CM viscosity is key. In general, viscosity of CM increases with higher CM concentration and is directly influenced by temperature: pre-warming CM leads to decreased viscosity, which may reduce the risk of both CM extravasation and adverse events in general, increasing participant comfort (14, 15, 17). However, the necessity to pre-warm CM for clinical CT applications is still under debate (8-13). Indeed, European and American guidelines on the use of CM are not in agreement on pre-warming CM (12, 13). The European Society of Urogenital Radiology recommends pre-warming iodine-based CM in all cases (13). On the other hand, according to the American College of Radiology, pre-warming CM is only necessary for concentrations of 370mg iodine per ml or higher, injection rates above 5ml/s, or if small-gauge catheters are used (12, 18, 19). The latter advice is primarily based on a large retrospective study by Davenport et al. comparing 12.682 injections with pre-warmed CM to 12.138 injections without pre-warmed CM (11). Adverse event rates were not different for iopamidol 300 injections of less than 6ml/s, but were significantly reduced by pre-warming for iopamidol 370 injections.

Pre-warming CM requires special equipment and more complex planning and logistics. On the other hand, pre-warming CM may yield higher attenuation levels, image quality and comfort (20). The question remains whether pre-warming CM is necessary when moderate flow rates (<6ml/s) are used, as is the case in abdominal imaging.

The aim of the study ContrAst media Temperature and patient Comfort in computed tomograpHY of the abdomen (CATCHY), was to prospectively

compare room temperature CM to pre-warmed CM with regard to image quality, safety, and participant comfort in portal venous abdominal imaging.

Materials and Methods

Ethics

This double-blinded randomized controlled non-inferiority trial was approved by the local ethics committee and the institutional review board, and is registered on ClinicalTrials.gov (NCT04249479). Written informed consent was obtained before inclusion in the clinical trial. The study did not receive any industry support.

Study design & Study Population

Using CM at room temperature (~23°C [~73°F]) might result in lower attenuation than would be achieved using CM pre-warmed to body temperature (20). The hypothesis of the CATCHY-trial is that using CM at room temperature does not compromise diagnostic image quality, patient safety or comfort in the setting of abdominal imaging. The sample size was calculated to enable detection of an absolute difference of 10HU in mean attenuation of the liver. This non-inferiority margin was chosen based on earlier studies where mean attenuation of 120HU was found sufficient and a decrease in attenuation of 10% was pronounced clinically significant (21). To be able to detect a difference greater than 10HU with a power of 90% and two-sided alpha of 5%, 98 participants per group are required. We recruited an additional 10% to account for potential loss to follow-up.

Participants referred for an abdominal CT in portal venous phase, were prospectively included between February and August 2020 at our center. Exclusion criteria were hemodynamic instability, pregnancy, renal insufficiency (estimated glomerular filtration rate <30 mL/min per 1.73m^2), prior adverse reactions to iodinated CM, age below 18 and inability to place an 18-gauge needle (22, 23). Additional scanning was no reason for exclusion unless it altered the underlying CM injection protocol. Repeated inclusion was allowed, as it was not expected to influence outcome. Body weight (kg) of the participant

was measured prior to scanning on a calibrated scale. As the maximum level of the dual head injector syringes is 200ml, participants with a body weight >115kg were excluded from this study. Participants' height (meters) was checked and Body Mass Index calculated. A 1:1 computer-generated randomization schedule was used (TENALEA, Trans European Network for Clinical Trials Services). Stratification factors were age (<60 and ≥60years) and weight (<75 and ≥75kg). Participants were equally divided in two groups by variable block randomization.

All data was collected by one blinded researcher (B.M.) using electronic case-report forms and checked by an independent study monitor. Patients were blinded as to the allocated treatment. A written questionnaire evaluating comfort was filled in by the participant directly after each CT exam.

Scan and contrast media injection protocol

A third-generation dual source CT scanner (Somatom Force; Siemens Healthineers, Forchheim, Germany) with automated tube current modulation (CareDose4D, Siemens) and automated tube voltage selection (CarekV; Siemens) techniques was used: 120kV_{ref} and 150mAs_{ref}, 192x0.6 mm slice collimation, gantry rotation time 0.5s.

Group 1 received CM at room temperature (~23°C [~73.4°F]) and group 2 received pre-warmed CM (37°C [99°F]). An 18-gauge catheter (Vasofix® Safety, B Braun, Melsungen, Germany) was placed by the radiographer in the participants' arm (e.g. antecubital vein, forearm or wrist) prior to scanning. For both groups, the CM injection protocol (300mg/ml [Iopromide; Ultravist 300; Bayer Healthcare, Berlin, Germany]) was adapted to the participants' body weight and the tube voltage used (at a tube voltage of 120, 110, 100 and 90kV a respective dosing factor of 0.521, 0.469, 0.417 and 0.365gI/kg was used) (8, 21). The scan was performed 70s after start of the CM injection using a dual head power injector (Stellant®; Bayer Healthcare, Berlin, Germany) followed by a saline flush with the same injection speed and an overall volume of 40ml.

Image reconstruction parameters were: 3mm slice thickness, 2mm increment, soft tissue kernel (Br40) and iterative reconstruction (IR) strengths 2/3 (Siemens; Advanced Modelled Iterative Reconstruction).

A dedicated data acquisition program (Certegra Informatics Solution; Bayer) monitored the CM parameters. Radiation dose and reconstruction settings were collected from the dose sheet at the PACS workstation (IMPAX version 6.6.1.5003; AGFA HealthCare N.V., Mortsel, Belgium).

Primary outcome

Absolute difference in mean attenuation of the liver parenchyma between groups was calculated with a two-sided 95% confidence interval (CI) of the difference. Mean attenuation in Hounsfield Units (HU) was based on three liver segments, preferably segments 2, 5 and 8 (Couinaud classification (24)). A region of interest was drawn in each segment (area: ≥1cm^2), not containing vessels, bile ducts or lesions.

Secondary outcomes

Objective image quality was rated using signal-to-noise ratio (SNR: mean attenuation divided by the mean standard deviation [SD]) and contrast-to-noise ratio (CNR: mean liver attenuation minus HU of the left paraspinal muscle, divided by the SD of the attenuation of the paraspinal muscle). Subjective image quality was rated in consensus on a 5-point Likert scale by two readers, B.M. and C.M. (5- and 10-years' experience in abdominal imaging, respectively). Readers were blinded to the allocated protocol. Overall image quality was rated on a 5-point Likert scale (1=excellent, 2=good, 3=moderate, 4=poor and 5=very poor) (21). Readers were allowed to level window settings individually.

All adverse events, including contrast extravasation, were reported by the radiographer.

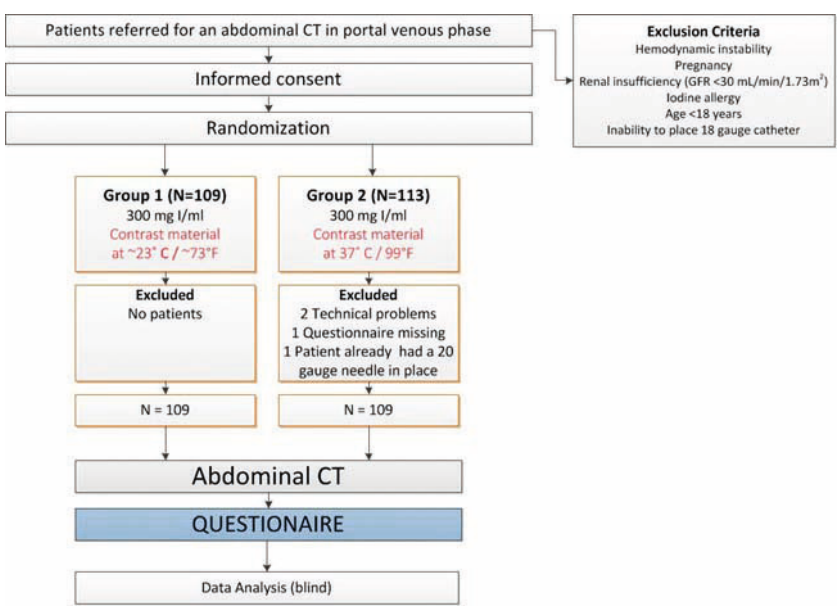
Comfort was rated by the patient on the questionnaire provided by the radiographer directly after the scan was performed (1=very bad, 2=bad, 3=neutral, 4=good, 5=excellent). An 11-point numeric rating scale was used to

evaluate pain during injection (0=no pain; 10=very severe pain) (17). Feelings of shivering, goosebumps or cold were evaluated and an open field was provided for the patient to record any other experiences. The questionnaire is given in the Appendix.

Statistical analysis

Dichotomous outcomes are reported as absolute numbers with percentages, continuous outcome variables are reported as means ±SD. Results are stratified by treatment allocation. To test for non-inferiority, a CI approach was used on an analysis of covariance (ANCOVA) model, with a two-sided 5% level of significance. For the primary endpoint, non-inferiority of room temperature CM to pre-warmed CM could be claimed if the lower limit of the CI for the absolute difference in mean liver attenuation (room temperature CM group minus pre-warmed CM group) falls above -10HU. This test for non-inferiority was only performed for the primary outcome.

Figure 1. Trial profile. Abbreviations: GFR, glomerular filtration rate.



Participant comfort and pain intensity were compared between groups using the Mann-Whitney U test. The $\chi 2$ test, and in case of expected cell counts

of less than five, Fishers exact test, was used for dichotomized variables. Continuous normally distributed variables were compared between groups using the independent samples t-test. The Mann-Whitney U test was used for not normally distributed variables. Data was analysed using statistical software (SPSS, version 26.0; IBM Corp., New York, NY). A two-sided P value <0.05 is considered statistically significant. Both per-protocol and intention-to-treat analyses were done.

Table 1. Key demographic and clinical characteristics of randomized groups.

Characteristics	Group 1 (Room temperature) N = 109	Group 2 (37°C [99°F]) N = 113
Excluded participants	0	4
Age (y)	66.3 ± 10.6	65.1 ± 11.1
Sex (% male)	56.0%	64.2%
Body weight (kg)	79.7 ± 13.7	78.4 ± 12.8
Height (m)	1.72 ± 0.09	1.72 ± 0.08
BMI (kg/m2)	26.8 ± 3.7	26.5 ± 4.0
Scan indication (%)		
Oncology	97.2%	92.7%
Infection	0.9%	2.8%
Other	1.8%	4.6%

Abbreviations: BMI, Body mass index.

Results

Baseline characteristics

Two-hundred twenty-two participants were enrolled. Four participants were excluded; two due to technical problems, in one participant the questionnaire form was missing, and one participant already had a 20-gauge needle in place and therefore had to be excluded (figure 1). All patients received their allocated treatment. Therefore, in this study, the intention-to-treat population is the same as the per-protocol population. Key demographic and clinical characteristics are detailed in table 1.

Table 2. Contrast media and radiation dose parameters.

CM and radiation dose parameters	Group 1 (Room temperature) N = 109	Group 2 (37° C) N = 109	P
CM volume (ml)	103.6 ± 21.7	100.8 ± 21.4	0.33
TIL (g)	31.1 ± 6.5	30.2 ± 6.4	0.34
Flow rate (ml/s)	3.4 ± 0.7	3.3 ± 0.7	0.31
Peak flow rate (ml/s)	3.8 ± 0.9	3.8 ± 0.8	0.89
Peak Pressure (psi)	63.1 ± 19.7	54.9 ± 18.4	0.001
IDR (gI/s)	1.0 ± 0.2	1.0 ± 0.2	0.33
Tube voltage (kV)			0.84
90kV (%)	64.2%	67.9%	
100kV (%)	33.9%	30.3%	
110kV (%)	1.8%	1.8%	
120kV (%)	0%	0%	
Mean mAsref	293.4 ± 55.9	300.7 ± 57.2	0.29
Mean mAseff	217.1 ± 51.6	208.4 ± 47.0	0.20
CTDIvol (mGy)	7.2 ± 2.3	6.9 ± 2.0	0.31
DLP (mGy*cm)	386.5 ± 133.6	390.4 ± 136.8	0.83
IR2(%) / IR3(%)	60.6% / 39.4%	54.1% / 45.9%	0.34

Abbreviations: CM, contrast media; TIL, total iodine load; IDR, iodine delivery rate; mAs_{ref}, quality reference mAs; mAs_{eff}, effective mAs, $CTDI_{vol}$, CT dose index; DLP, dose length product; IR, Iterative reconstruction. CM volume, TIL, mAs_{eff} and DLP, mean liver attenuation (HU), SNR and CNR were normally distributed and compared using the independent samples T-test. Flow rate, peak flow rate, peak pressure, mAs_{ref} and $CTDI_{vol}$ were not normally distributed and the Mann-Whitney U test was used.

Mean CM volume was 103.6±21.7ml in group 1 and 100.8±21.4ml in group 2 (P=0.33). Mean flow rate was 3.4±0.7 in group 1 and 3.3±0.7ml/s in group 2 (P=0.31). Other CM and radiation dose parameters are shown in Table 2. There were no significant differences between groups, except peak pressure (in psi) which was significantly higher in group 1: 63.1±19.7psi (room temperature CM) versus 54.9±18.4psi (pre-warmed CM) (P=0.001).

Primary outcome

The percentage difference in mean attenuation (group 1 minus group 2) was +4.23HU with 95% CI +0.35 to +8.11. The lower limit of the CI of the difference

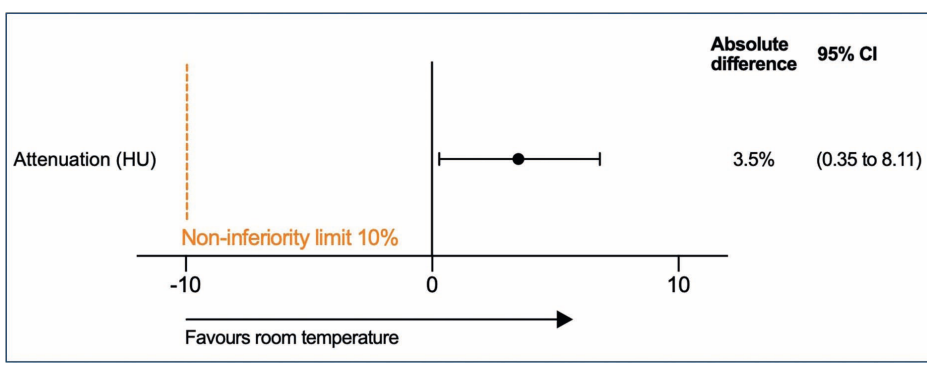
falls within the non-inferiority margin, indicating non-inferiority of room temperature CM with respect to attenuation (figure 2).

Secondary outcomes

Objective and subjective image quality results are shown in table 3. Mean attenuation was 122.2±13.1 in group 1 and 118.0±15.9 in group 2 (p=0.03). SNR, CNR and subjective image quality did not significantly differ between groups (P=0.53, 0.23 and 0.99 respectively).

There was one person with a contrast extravasation in group 2. No other adverse events were reported.

Figure 2. Absolute difference in mean attenuation of the liver (room temperature CM group minus pre-warmed CM group). The dashed line shows the non-inferiority margin, set at -10HU. Error bars indicate the 95% confidence interval (CI) of the difference; the bullet shows the point estimate. Abbreviations: HU, Hounsfield Units.



Patient comfort and pain results are shown in table 4. Comfort scores were higher in group 1 than in group 2 (P=0.03). Comfort was graded excellent or good by 91.7% of the participants in group 1 and by 86.2% of the participants in group 2. Comfort was rated bad or very bad by 1 participant (0.9%) in each group. In group 1 three patients (3.3%) and in group 2 four patients (4.4%) perceived pain (P>0.99). Pain intensity scores were not significantly different between groups (P=0.20). Four participants had a feeling of being cold, of which three were randomized in group 1 (table 4).

Table 3. Objective and subjective image quality.

	Group 1 (room temperature) N = 109	Group 2 (37°C [99°F]) N = 109	P
Objective image quality			
Mean Attenuation (HU)	122.2 ± 13.1	118.0 ± 15.9	0.03
SNR	9.8 ± 2.1	9.6 ± 2.1	0.53
CNR	6.2 ± 2.4	5.8 ± 2.2	0.23
Subjective image quality			
Excellent (%)	26.6%	25.7%	0.99
Good (%)	66.1%	66.1%	
Moderate (%)	6.4%	7.3%	
Poor (%)	0.9%	0.9%	
Very poor (%)	0%	0%	

Abbreviations: HU, Hounsfield Units; SNR, signal-to-noise ratio; CNR, contrast-to-noise ratio.

Table 4. Participant comfort.

Comfort	Group 1 (Room temperature) N = 109	Group 2 (37°C [99°F]) N = 109	P
Contrast extravasation	0	1	
Comfort (median, IQR)	4 (4-5)	4 (4-5)	0.03
Excellent (N)	54	39	
Good (N)	46	55	
Neutral (N)	8	14	
Bad (N)	1	0	
Very bad (N)	0	1	
Pain intensity (median, IQR)	0 (0-0)	0 (0-0)	0.20
Pain (yes/no)	3/106	4/105	>0.99
Feeling cold			
Shivering (N)	0	0	
Goosebumps (N)	0	0	
Cold (N)	3	1	

Abbreviations: IQR, interquartile range.

Discussion

CM at room temperature was found to be non-inferior to pre-warmed CM in mean attenuation of the liver. Furthermore, the present study found no evidence or benefits from pre-warming iodinated CM with regard to image quality, safety and patient comfort in portal venous abdominal CT imaging. Mean attenuation was significantly higher in the room temperature CM group. Differences in SNR, CNR and subjective image quality between groups were small and non-significant. Injecting CM at room temperature did not result in CM extravasations or other adverse events at the given IDR of 1.0gI/s, which is in line with the results of the study by Davenport et al. (11-13). CM at room temperature yielded significantly higher participant comfort scores, although absolute differences are small and may not be clinically relevant.

This is the first prospective randomized trial providing high level evidence that participant comfort and image quality are not increased by pre-warming CM in this setting. The European and American guidelines have a conflicting opinion on this subject (12, 13). Based on the results of the current study it appears that the American College of Radiology guidelines is the one to follow. CM extravasation, other adverse events and participant comfort are not adversely affected by administering CM at room temperature. As a consequence, one may forego pre-warming for CM injections with low iodine concentration of 300mg/ml, at moderate flow rates and a catheter of 18-gauge.

Peak pressure was significantly higher for CM at room temperature compared to pre-warmed CM. Mean flow rate in present study was quite low (mean flow rate of 3.4ml/s ranging from 2.0ml/s up to a maximum of 5.3ml/s). A higher flow rate is expected to further increase peak pressure and therefore might negatively influence participant comfort. However, at our center more than 90% of the scans performed between 2013 and 2019 had a flow rate below 6ml/s with rather low psi and IDR values, and the results of the current trial will apply. Accordingly, future research could focus on participant comfort when CM is injected at room temperature with higher flow rates, for example in cardiovascular imaging. As shown by Davenport et al. increasing flow rates increases incidences of CM extravasation and other adverse events in specific settings, most likely also decreasing participant comfort (11).

The study has some limitations. First, it is a single-center randomized controlled trial. Generalizability to other centers might be limited. Intra-individual comparison may have been preferable but is not readily feasible in clinical setting. Second, the sample size was based on a non-inferiority margin for objective image quality, because not much is known about patient comfort margins, which was the main study outcome. In addition, CM temperature was measured in the bottle. Pre-warmed CM might cool down when travelling through the tubing from the bottle to the patient. Therefore, injected CM temperature may have been overestimated. Lastly, the mean flow rate was quite low and results might have been different if a CM injection protocols with higher flow rate were used.

Pre-warming CM is not beneficial in terms of image quality, safety, and participant comfort in portal venous phase abdominal CT imaging. Pre-warming CM should therefore not be a pre-requisite in state-of-the art injection protocols for parenchymal imaging for CM injections with low iodine concentrations, at moderate flow rates and a reasonable catheter size.

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Appendix

Patient comfort assessment questionnaire. Note that this is a translation, as the original questionnaire was in the native language (Dutch).

Patient comfort assessment form **CATCHY trial, nr CATCHY .....**

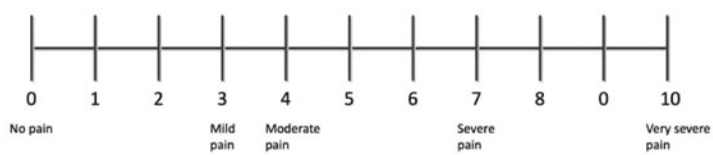
How would you grade comfort during injection?

1 = very bad
2 = bad
3 = neutral
4 = good
5 = very good

Grade: .....

Did you feel any pain during injection Yes / No

If yes, how would you grade the intensity of the pain?

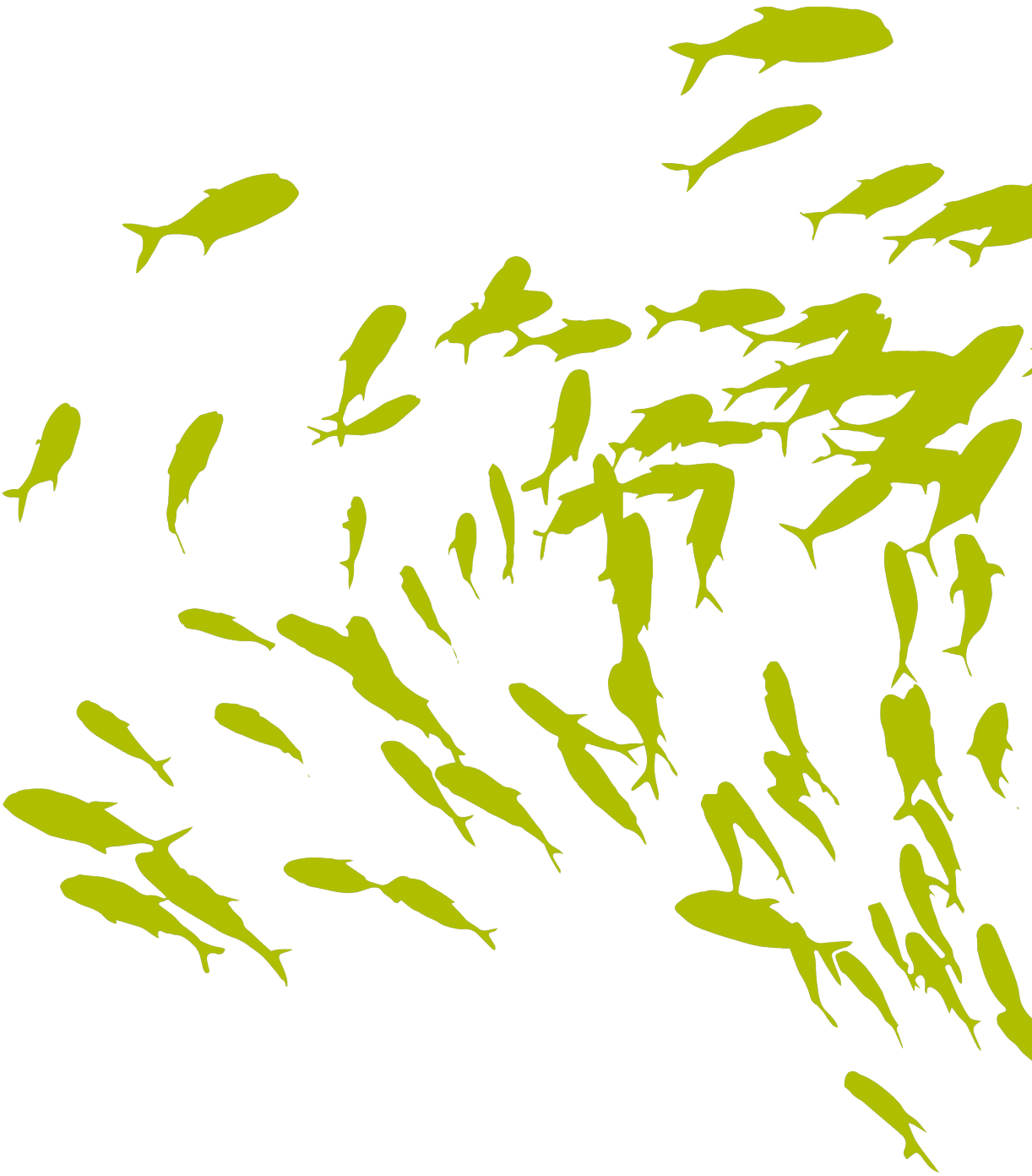


Did you experience any of the following feelings (Tick the box, multiple answers possible)?

- ○ Shivering
- ○ Goose bumps
- ○ Cold
- ○ Other.....

Do you have any other comments or remarks regarding the procedure?

- ○ Yes.....
  .....
  .....
- ○ No other comments



CHAPTER 7

Tailoring contrast media protocols to varying tube voltages in vascular and parenchymal CT imaging

The 10-to-10 rule

B. Martens*, B.M.F. Hendriks*, C. Mihl, J.E. Wildberger

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Abstract

The latest technical developments in CT have created the possibility for individualized scan protocols, using variable kV settings. A lower tube voltage draws closer to the iodine K-edge, increasing iodine attenuation, compared to a higher tube voltage. In addition, attenuation is influenced by patient characteristics such as total body weight. Therefore, in order to maintain a robust contrast enhancement throughout the patient population in both vascular and parenchymal CT scans, one must adapt the contrast media (CM) protocol to the kV setting and the patient body habitus. This paper presents current evidence and proposes a simple rule-of-thumb for adjusting the CM protocol in both vascular and parenchymal studies; the 10-to-10 rule.

Key words

Computed tomography; Contrast media; Radiation Dosage; Abdomen; Pulmonary artery; Coronary vessels; Aorta.

Introduction

Since the development of the first computed tomography (CT) scanner in 1967, the technology of these scanners has evolved (1). The advent of powerful x-ray tubes, multiple detector rows and dual source technology has led to short acquisition times and excellent temporal and spatial resolution (2).

CT nowadays is a widely available, versatile and fast medical imaging method which has revolutionized radiology and the field of medicine as a whole (3). In the era of personalized medicine, we are increasingly deviating from the "one size fits all protocol" and moving towards scan and contrast media (CM) injection protocols tailored to the individual patient.

The paper summarizes the most relevant factors in CM protocols for optimal attenuation in parenchymal CT and CT angiography (CTA). It proposes an easy-to-use rule of thumb (the 10-to-10 rule) for tailoring CM injection protocols to variable kV settings (4-6). When used in conjunction with personalized CM protocols, a homogeneous image quality throughout the patient population can be achieved.

Individualized scan protocols

A comprehensive overview of the latest technical developments in CT has recently been published by Lell *and colleagues* (3). The latest tube technology allows for higher ion flux during longer acquisition times; this translates in clinical practice to lower kV scanning and lower radiation dose for most patients (2). Automated tube current modulation (ATCM) is a technique used often in daily clinical practice and recently the automated tube voltage selection (ATVS) technique was introduced. These advances in CT technology create the opportunity for radiation dose tailoring to each individual patient and scan indication (7, 8). Where a large adult might be scanned at 120 kV in order to achieve good image quality, a smaller person may be scanned using a tube voltage as low as 70 or 80 kV and concordantly the tube current is adjusted in order to achieve similar image quality with a subsequent lower radiation dose. The possibility for low kV scanning is advantageous for lowering the

hypothetical radiation-induced cancer risk for patients and follows the "As Low As Reasonable Achievable" (ALARA) principle (9).

Individualized contrast media protocols

In parenchymal studies the total volume is most important for reaching optimal liver enhancement, while previous studies have indicated that the iodine delivery rate (IDR, in g I/s) is the decisive factor for determining intravascular enhancement in vascular CT (10). This concept has been proven for CTA of the pulmonary arteries (CTPA), coronary CTA (CCTA) and CTA of the aorta (11-14). The relationship between IDR, flow rate and CM concentration can be explained with the following formula: IDR (g I/s) = [CM] (g I/ml) * flow rate (ml/s). Normalizing IDR is a straightforward approach to make different injection protocols comparable. As seen in the formula, IDR can be modified either by adapting flow rate or adapting CM concentration.

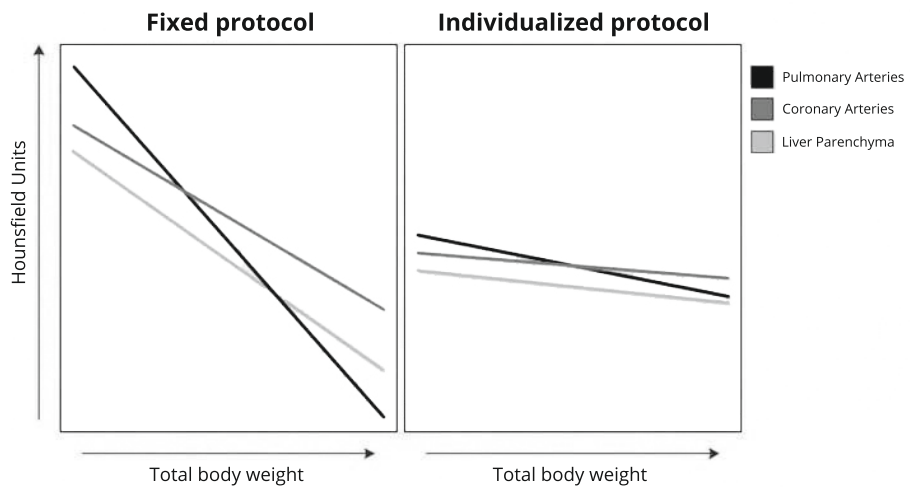
Several patient factors are known to influence the attenuation of both vascular and parenchymal structures. Patient body weight is a well described influential factor in CM application (15). In coronary and pulmonary arteries and the liver parenchyma, adapting the CM volume to the patients' weight has proven to be beneficial (see figure 1) (13, 16, 17). Adapting the volume to the total body weight (TBW) results in a more homogeneous attenuation of pulmonary and coronary arteries and the liver parenchyma, between patients,

in comparison to a fixed 'one size fits all' CM injection protocol. An individualized CM injection protocol also turned out to reduce CM usage in general, while reaching optimal enhancement levels (13, 16, 17).

It is possible to individualize CM injection protocols based on TBW as mentioned above, but factors as lean body weight (LBW), body mass index (BMI) and body surface area (BSA) are also parameters widely studied (18). LBW is TBW minus the amount of fat the body contains, with the underlying idea that fat is less vascularized compared to muscle (10). Therefore, considering this concept, fat should not be taken in to account when calculating the optimal amount of CM that should be given to a specific patient. LBW can be calculated by using

either the James or the Boer formula, of which the latter is the first choice in obese patients (19).

Figure 1. Individualized contrast media injection protocols based on body weight, compared to a fixed injection protocol in the pulmonary arteries, the proximal coronary arteries and in the liver parenchyma. The figure depicts more similar and robust enhancement of both vascular and parenchymal structures with individualized protocol (modified from: 10, 13, 14 and presented schematically).



Combining scan- and contrast media protocols for optimal image quality

With lower tube voltages and therefore the x-ray output drawing closer to the 33 keV k-edge of iodine, the photoelectric effect increases which in turn increases the attenuation of iodine (10). This provides new opportunities for CM individualization in both arterial and parenchymal studies. The benefits of lower kV scanning are twofold. First of all, it allows for the possibility of reducing the total amount of CM, hypothesized to be beneficial in preventing contrast-induced nephropathy (20, 21). Some controversy remains on whether intravenous application of CM causes the sometimes observed and reversible dip in renal function (22, 23). Nevertheless, there is simply no need to give patients more CM than needed, especially as the underlying physiological effects are still not fully understood.

The use of variable, individualized kV-settings with the arrival of ATCM and ATVS techniques, comes with a new challenge; the variety in kV settings used

have a substantial impact on the attenuation of iodine. If the iodine k-edge effect is not taken into account, the CT attenuation numbers and thereby image quality in a patient population scanned with different tube voltage settings is heterogeneous (11). Radiologists incorporate attenuation characteristics when drawing conclusions from CT images. For example, the assessment of lesions to be more likely benign or malignant depends on the attenuation pattern (24, 25). With a large variety of tube voltages used and a great diversity in CM volumes and patient characteristics in daily clinical practice, it is important to reach a comparable enhancement of the target structure, regardless of these factors. Only when attenuation is similar and robust between patients, reliable conclusions can be drawn from radiological imaging.

Several groups have investigated the effect of low kV scanning on attenuation values during CTA and parenchymal CT (16, 18, 26-28). At present, one important enigma remains; how to correctly apply patient-specific, tube voltage tailored CM protocols for each clinical indication and scan technique. The possibilities of lowering the kV setting and the methods of concordantly adapting the CM parameters have been studied widely. The same accounts for the patient-specific individualisation of CM protocols. The authors combined the various findings of these studies into a practical, easy to remember, rule of thumb: the 10 to 10 rule.

Rule of thumb: The 10 to 10 rule

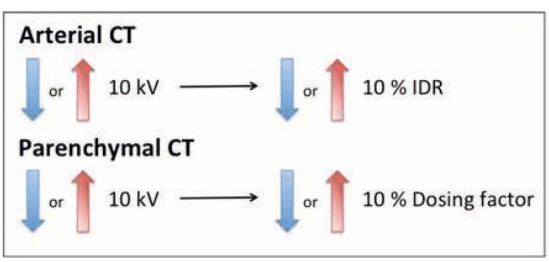
Several IDR reduction percentages have been proposed when trying to adapt the vascular CT protocol to the different tube voltages used and some have been validated in a clinical setting (4, 28, 29). When looking closely at the available literature there is some overlap in previously described methods, which can be boiled down to a rule-of-thumb: In CTA one may roughly deduct 10 % of the IDR per 10 kV step down and vice versa. A straightforward way to adapt the IDR is by changing the flow rate, however can also be achieved by altering the concentration of iodine in the CM. This rule has been validated in clinical practice for CTPA and CCTA (4, 5).

In parenchymal studies a reduction of 10 kV should result in a 10 % reduction in total iodine load (TIL) (30). The landmark paper by Heiken et al. from 1995 stated

that an attenuation increase of ≥ 50 HU of the liver parenchyma is necessary to ensure appropriate visibility of low-attenuating lesions, based on a tube voltage of 120 kV (31, 32). To achieve this attenuation, a dosing factor of 0.521 grams of iodine per kilogram (g I/kg) can be calculated (31). A recent study showed that a 10 kV reduction should lead to a 10 % decrease of the dosing factor and vice versa, to be able to individualize the parenchymal CT based on both patient and scanner characteristics (6, 33).

This 10-to-10 rule can easily be applied to any existing patient tailored protocol, thereby adjusting the CM protocol for any kV setting and individual patient characteristics (see figure 2).

Figure 2. The rule of thumb.

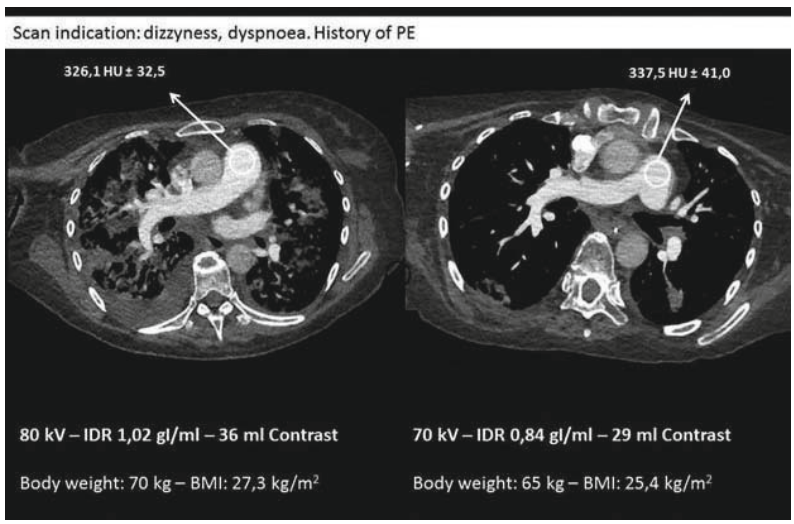


Example I: Vascular studies

When a patient is scanned with a reduced tube voltage of 70 kV, where normally 120 kV is used, one may decrease the IDR by 50 % (34). When the same concentration of CM is used, this could mean a 50 % reduction in flow rate. A 50 % decrease in flow rate at a constant injection time will also lead to a reduction in total CM volume and thereby the TIL received by the patient. In addition, keeping the injection time constant ensures it to be a robust and reliable method to be used 24/7.

Figure 3 is an example of the same patient scanned twice with different kV settings and adapted IDR, which resulted in a similar enhancement of the pulmonary arteries (4).

Figure 3. Two CT pulmonary angiography scans performed in the same patient because of possible pulmonary embolism. The iodine delivery rate (IDR) is adapted to the different kV setting used in each scan; 80 kV with an IDR of 1.02 g I/s for scan A and 70 kV with an IDR of 0.84 g I/s for scan B. The region of interest (circle) in each scan shows the comparable Hounsfield Units per scan despite the different kV setting used.

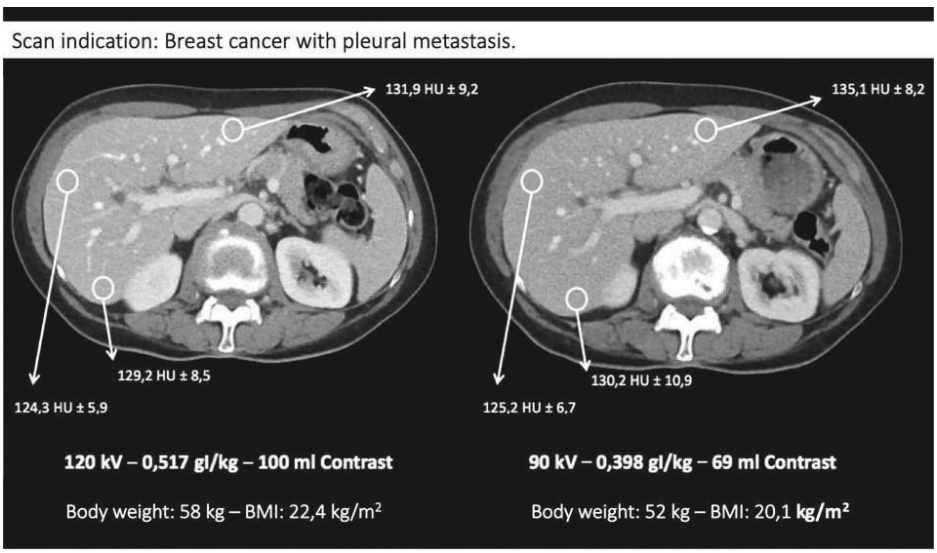


There is more than 10 % reduction in IDR, because the patient lost weight between scan A and B; around 5 kg, which the IDR was also adapted for in this case (4).

Example II: Parenchymal studies

Figure 4 depicts a case where a patient is scanned twice with approximately one year in between. The scans are both performed on a 3rd-generation dual source CT scanner (Somatom Force, Siemens Healthineers, Forchheim, Germany), the first at 120 kV and the second at 90 kV. This resulted in similar attenuation values, because the CM dosing factor is adapted accordingly. A 30 kV tube voltage reduction resulted in a 30 % decrease of the dosing factor. Injection time is held constant at 30 seconds. Therefore, the flow rate changes with a changing body weight (6).

Figure 4. Two abdominal CT scans of the same patient in portal venous phase, performed on the same scanner at different kV settings. The attenuation remains the same, by adapting the total amount of CM administered to the kV setting and the patients' body weight. The scan on the left is performed at 120 kV and the one on the right at 90 kV with one-year time difference on a 3rd-generation dual source CT scanner (6).



Conclusion

The 10-to-10 rule is an easy to use rule of thumb to adjust CM injection protocols to varying tube voltages. When used in conjunction with patient tailored injection protocols, this rule will aid in keeping image quality constant and homogeneous throughout a patient population.

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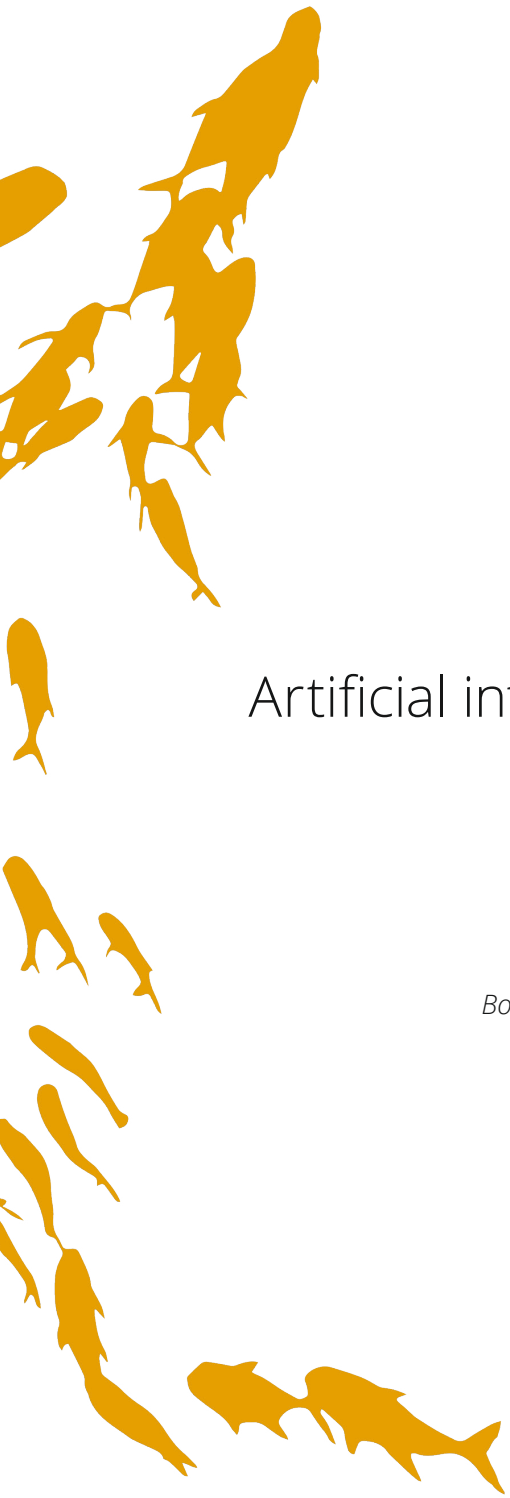

CHAPTER 8

Book chapter: Artificial intelligence based contrast medium optimization

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Abstract

Contrast media (CM) application is important for the evaluation of the heart with both computed tomography (CT) and magnetic resonance imaging (MRI). In many hospitals around the world, CM is still used in a "one size fits all" fashion, usually with a "safety margin" regarding CM volume, guaranteeing sufficient enhancement even in the heavier patient. The primary reason for using standard protocols instead of optimising CM for individual patients is the fact that CM administration is still largely a manual action, time consuming and regarded as sensitive for errors. Artificial intelligence (AI) techniques could play a role in that respect. If AI can select the optimal CM injection protocol for the specific patient, on a particular CT or MRI scanner for the clinical scan indication, AI would improve both patient care and workflow. Different aspects might extend the study or make the study more difficult, e.g. patient anxiety, difficult venous access and/or an irregular heartbeat. In case these factors could be taken into account when scheduling the examination, that would further improve workflow. In addition, AI might help in further reducing CM, scan time and – in case of CT – radiation dose. The position of AI with regard to CM optimisation is not thoroughly studied yet, this chapter aims to offer insights into possible future directions.

Keywords

Computed Tomography; Diagnostic Imaging; Coronary artery disease; Contrast Media; Weight; Artificial Intelligence; Heart

Background in scan and contrast media protocols

Coronary CT angiography (CCTA) has a very high negative predictive value for ruling out coronary artery disease (99 %) (1). Sufficient intravascular enhancement of the coronaries (> 325 Hounsfield Units [HU]) is necessary to reach diagnostic accuracy (2). The k-edge of iodine lies at 33 keV and when the tube voltage approaches the k-edge, the attenuation of iodine increases (3). This makes it possible to increase the vascular or parenchymal enhancement by decreasing the tube voltage of the scan acquisition. Different parameters can be adapted to reach sufficient enhancement of the coronaries in each patient on every occasion. First of all, the iodine delivery rate (IDR) is considered the most decisive parameter for attenuation of vascular structures (4, 5). Second, a body weight adapted CM injection protocol results in more homogeneous enhancement of the coronary arteries, compared to a one size fits all protocol (6). Lastly, the 10-to-10 rule optimizes the CM application even further based on the tube voltage used: a 10 kV reduction should be followed by a 10 % reduction in IDR and vice versa (7). To optimize CM timing, a test bolus or bolus tracking technique can be used (8). For the test bolus method, multiple low dose axial image slices are acquired at one point on the z-axis after the injection of a small amount of CM. The test bolus is injected with the same flow rate and concentration as the main bolus. This creates a time-enhancement curve where the peak-enhancement can be determined, to find the optimal timing for the scan. The time to peak is used as an estimated scan delay for the scan with the main CM dose (9). For bolus tracking, CM is injected and attenuation is measured in a predefined vessel until a threshold is reached. Once the attenuation reaches the threshold, the scan starts after a predefined fixed delay (10).

There are three different cardiac scan acquisition modes, ECG triggered or flash (high-pitch mode), prospective ECG gated (step and shoot) and retrospective ECG gating (helical). Based on heart rate and heart rhythm, a specific protocol is chosen (11).

Iterative Reconstruction (IR) techniques, automated tube current modulation (ATCM) and automated tube voltage selection (ATVS) are at present incorporated in daily clinical routine. These techniques are performed semi-automatically,

as they have to be approved by a radiographer, and generally do not fall under the topic of AI. CM injectors that combine scanner protocol information (e.g. tube voltage and tube current selected by ATCM and ATVS) with the patient characteristics and clinical question are a promising tool for automatically optimising CM application but are yet to be developed and synchronised. To date, individualising CM injection protocols is still largely a manual and time-consuming action, which explains the preference for a standard "one size fits all" protocol in many centres.

Artificial Intelligence for Contrast media optimisation

Because of technical developments the cardiac CT scan duration nowadays is very short, ranging from several seconds to sub-second imaging. For imaging of the coronary arteries, a fast scan acquisition is beneficial, as this makes imaging of the whole heart possible within one heartbeat, subsequently reducing radiation and CM dose. Faster scanners and shortened CM protocols result in more critical scan timing, as the chance of missing the peak enhancement increases, especially with respect to the vascular structures (9, 10, 12). AI could improve coordination of scan and CM timing, resulting in optimized CM and radiation dose in each individual patient.

The possibility to perform thoracic scans in a single heartbeat reduces motion artefacts and cardiac structures can nowadays often be assessed on a regular CT of the chest (12). Image quality might be sufficient to evaluate the heart, although on a regular chest CT there might be not enough CM distribution in the cardiac chambers. Suboptimal cardiac enhancement is not surprising, as a dedicated cardiac scan is performed later after start of CM injection than a regular CT of the chest (13). As a result, information regarding cardiopathies and valvular changes stay hidden.

A triple rule out protocol has been advocated as a solution for better cardiac image quality on chest CT's (14). AI however may bypass the additional CM volume of a triple rule out CM protocol and it could bypass the need for CM entirely. A deep convolutional neural network (DCNN) has shown to be beneficial in these areas too (15). Santini et al. developed a DCNN capable of producing contrast-enhanced CT (CECT) images out of a non-contrast image

of the thorax by mimicking the human visual system with the created network (15). The left cardiac ventricle was delineated by the software on the non-CECT images, leading to the synthesized CECT image. Non-contrast images where compared to real CECT images and the synthesized CECT images. A Normalized Mutual Information index (NMI) was used to quantify the capability of the model to create a synthesized CECT close to the real CECT. The Dice index is a statistical tool that compares the similarity between two datasets and was used to evaluate the estimation of the cardiac ventricles. The synthesized compared to the real CECT images gained a good similarity (NMI of 0.93 ± 0.03) and extraction of the left ventricle was possible (Dice = 0.88). Therefore it was possible to subtract the left cardiac ventricle from a non-CECT image and, in addition, to provide volumetric information of the heart on a regular thoracic CT (15). Mannil et al. used texture analysis and machine learning to detect a myocardial infarction on an unenhanced low radiation dose cardiac CT (16). Both DCNN and machine learning turn out to be capable of retrieving latent information from a non-CECT image. As information about the cardiac ventricles can be subtracted from non-CECT images, it seems to be a small step to generate an optimal contrast-enhanced coronary image of a CT with reduced CM dosing or scans with alternative CM timing (such as chest CTs).

In current clinical practice, total CM volumes containing as little as 9 grams of iodine can be used for CCTA with diagnostic image quality. Further reduction of CM might not be necessary for the protection of kidney function (17). However, it should be pointed out that reducing the amount of CM also decreases health care costs. Furthermore, iodinated CM reaches the groundwater and has an influence on the environment as well (18). AI could play a big role in aiding wide acceptance and implementation of individualised CM protocols, by fully automating the process of CM individualisation. This individualisation might be beneficial for advanced data-characterisation algorithms, such as radiomics. Differences in, for example, cardiac output and CM injection protocols influence the distribution of the CM in tissue. In addition, differences in scan acquisition parameters might influence spatial analysis (19). Therefore, differences in scan and CM protocols can influence features derived from radiomics algorithms. In order to optimally apply radiomics in the future, it seems vital that scan and injection protocols become comparable between hospital and countries.

Takumi et al. used bolus tracking data of previous CT scans of the same patient in dynamic liver imaging. The authors showed that a scan delay based on previous bolus tracking data resulted in a similar CM enhancement. Previous bolus tracking data could be used in following scans, shortening exam time and reducing radiation exposure (20). However, this will be more challenging to apply in cardiac imaging, as various different factors (e.g. medication, disease, patient stress level and time of the day) will influence cardiac output.

Uniformity of the CM protocol throughout the different hospitals in the world, could lead to optimal (coronary) enhancement in each patient, every time. In addition, by individualising and optimising CM injection protocols all around the world, attenuation of the targeted structures should become more uniform, which could be beneficial for future AI techniques.

Artificial Intelligence for Contrast Media Injection Protocol selection

Scan duration and therefore the CM injection protocol for both the prospective and retrospective ECG gated protocol are longer than for the ECG triggered (flash) protocol to ensure optimal enhancement of the coronaries. Having three different cardiac scan protocols makes the individualisation of scan and CM protocols even more complex.

An irregular heartbeat can complicate the selection of the right protocol. Problems in synchronisation of ECG signal with data acquisition sometimes result in non-diagnostic image quality necessitating scan repetition, with no guarantee of the second scan being of diagnostic image quality. AI could learn to recognise specific heartbeat patterns and select the appropriate scan protocol. Moreover, while determining the best scan protocol for the individual patient, the AI model should be capable of selecting the appropriate CM injection protocol on the available scanner for the specific question at hand. Notably, bolus tracking with a fixed trigger delay could miss peak enhancement in patients with a very high or very low cardiac output, because it does not take patient specific cardiovascular parameters output into account (9, 10). AI and machine learning algorithms could be applied to individualize trigger scan delay when using bolus tracking. Hinzpeter et al. proposed to use at least four bolus tracking enhancement values to evaluate the CM dynamics in the individual

patient. This information can be used to match the data to the available enhancement curves in an online database containing different arterial blood circulation curves. Thereby the optimal scan timing could be determined based on the best suited enhancement curve for each patient (10, 21).

Ideally, AI will suggest the most appropriate protocol so suboptimal image quality and repeated scanning can be a thing of the past. In addition, it would be of great value if it were possible to predict whether a prospectively ECG gated acquisition will be executed smoothly. For example, an AI algorithm capable of predicting that an extra systole will lead to a longer scan time, can adapt the CM bolus mid-scan to ensure sufficient enhancement throughout the whole scan duration.

AI-based Image reconstruction techniques

As mentioned before, decreasing the tube voltage is advantageous for both radiation and CM dose. However, it comes at the expense of increased image noise. Noise reduction algorithms offer dedicated opportunities in this respect. A knowledge-based IR algorithm minimizes the difference between measured raw CT data and the estimated image, by a penalty-based cost function (22). It decreases image noise and increases the contrast-to-noise ratio (CNR) (23). Wang et al. evaluated an AI-based noise reduction algorithm based on a DCNN (24). Their AI-based noise reduction algorithm based on 40 CT scans of the aorta at normal dose and at a simulated low dose. The dedicated algorithm learned that the output was input minus noise and, in this way, was able to generate noise reduced images. The algorithm improved image quality of the aorta, facilitating a 50 % CM dose reduction (24).

Another possibility for radiation and CM reduction lies in the large portion of follow-up CT scans performed on a daily basis, for example for oncological patients. These patients undergo repeated scanning of the same anatomical region. Therefore, shared anatomical information between those scans is available. This information can be used in an IR algorithm to significantly improve the diagnostic image quality (25). In the future, it might become possible to use the anatomical information from scans performed for a different indication, for a scheduled cardiac scan of the same patient, thereby reducing both radiation

and CM dose. This could lead to both scan and CM protocol optimisation as well as improvements in workflow.

Non-calcified and low attenuating plaques are more prone to future events than calcified plaques, as calcifications might stabilise the coronary plaque (26). In addition, positive remodelling, spotty calcifications and the napkin-ring sign are indicators of a high-risk plaque (27). Occasionally, some rather big differences in interpretation between readers can be present and especially blooming artefacts hamper the interpretation of soft plaques. In that respect, subtraction techniques might be promising for reducing these blooming artefacts (28). Differences in scan quality, CM application but also the experience of the reader and the subtlety of the findings will influence subjective evaluation of the CCTA (29). AI techniques could be helpful in standardising plaque interpretation and might even go a step further in determining plaque characteristics (27, 30).

Workflow

Scheduling a CT or MRI scan is often a job done by the supportive staff in the radiology department. It is time consuming and prone to errors. AI algorithms could be used to plan and schedule this medical care (31). The selection of the correct imaging modality, scan and CM injection protocol, as well as the ideal study date (e.g. should the scan be performed within an hour or a month) are parameters to keep in mind, when scheduling an exam. A task that might be difficult and prone to changes, but could be rather easy for an AI algorithm. This automated scheduling could involve prioritising patients and selecting the optimal imaging technique (e.g. ultrasound, CT or MRI) (31).

Information from previous studies could be taken into account. Anxious patients, known risk factors for CM related unfavourable outcomes, difficulty with obtaining venous access or a known irregular heartbeat (with exception of paradoxical atrial fibrillation, which is often not predictable) could be known upfront. This information could be used to select specific time slots for the requested CT or MRI exam. Predicting the scan type and scan duration correctly will improve efficient use of scanners and staff (21). Altogether, this optimized workflow will lead to improved patient care.

Red flags

The minimal diagnostic vascular enhancement for the coronary arteries, aorta and the pulmonary arteries are well studied (32). An attenuation below the threshold might result in non-diagnostic image quality, but when the enhancement is too high, CM can lead to artifacts mimicking relevant findings, making image quality suboptimal as well. For each target (vascular structure), it is possible to define an attenuation range for each CT exam. In case the limit is not reached or if the diagnostic HU level is exceeded, the study is regarded as suboptimal. It might be possible to exclude gross pathologies on images with suboptimal attenuation of the designated structures, but there is an increased risk that significant findings might be missed or misinterpreted. Factors such as motion artefacts, irregular heartbeat and unintentional incorrect scanner and/or injector settings might result in an unanticipated insufficient image quality (33). Ideally, an algorithm could approve image quality before the patient leaves the scanner room. The program should be capable of determining whether the coronary attenuation is sufficient and if artefacts are present that influence the interpretation significantly.

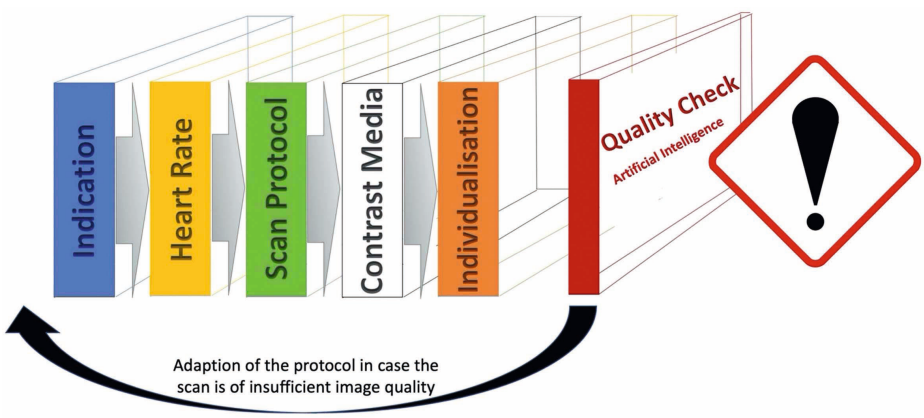
On some occasions an outpatient CT or MRI scan might be in a worklist for several days, while the scan shows unexpected pathology requiring immediate attention. AI could be trained to recognise and 'flag' a scan when unexpected clinically significant findings are indicated that should be reviewed right away. For example, a significant unstable coronary plaque, an aneurysm or dissection of the ascending aorta or an imminent cardiac tamponade could trigger an alarm signal notifying the radiologist to look at this exam immediately.

Summary

AI might be able to contribute to quality insurance by determining an individualized CM, scan and reconstruction technique in each patient. The scan could automatically be followed by an attenuation check of the targeted structure and a warning signal in case of any pathology present that is in need of immediate attention (figure 1). One step further, it would be valuable if AI could determine which parameters to adjust and to what extent to reach a

sufficient image quality when the first or any previous scan was regarded as non-diagnostic.

Figure 1. The role of artificial intelligence (AI) in contrast optimisation. The process starts with scan indication, followed by heart rate, which will influence which scan protocol is most appropriate. Next, the corresponding contrast media (CM) protocol is selected and aligned with individual patient parameters. The process ends with a quality check. If quality is insufficient, the process will iterate to improve scan and CM protocols based on errors and specific characteristics from previous exams. After image acquisition the process is followed by an automated search for urgent findings which may require immediate attention.



AI could be useful in individualising CM protocols based on patient and scanner characteristics as well as on suspected clinical pathology to improve both, daily clinical care and workflow. Although, in that respect, the question rises if this might be applicable in the near future because of legal considerations: who is taking the responsibilities if something goes wrong? This leads to an ethical discussion that will have to take place before AI can become widely incorporated in medical imaging. The example of self-driving cars sets out the grey area clearly. Who is responsible when a bystander gets hurt, can the self-driving car be responsible? Compared to a human, the car will probably not be able to make a morally guided decision, when an accident is about to happen. Because of these discussions, the introduction of self-driving cars did not happen yet (34). AI taking over the radiologists' job is ethically not so easy either.

One frequently reappearing topic of discussion involves AI taking over the radiologists' job. According to Geoffrey Hinton, no more radiologists should be trained, because deep learning would outperform the radiologist within 5 years, stated in 2016 in Toronto (35). As long as AI is seen as a potential threat, we might miss all the opportunities it has in store for us. This chapter has pointed out the possibilities of a DCNN, machine learning and deep learning as a tool for CM optimalisation in both CT and MRI. These kinds of applications could be used to improve workflow, image quality and even diagnostic capabilities. The future of radiology is bright, if we adopt the opportunities AI offers early.

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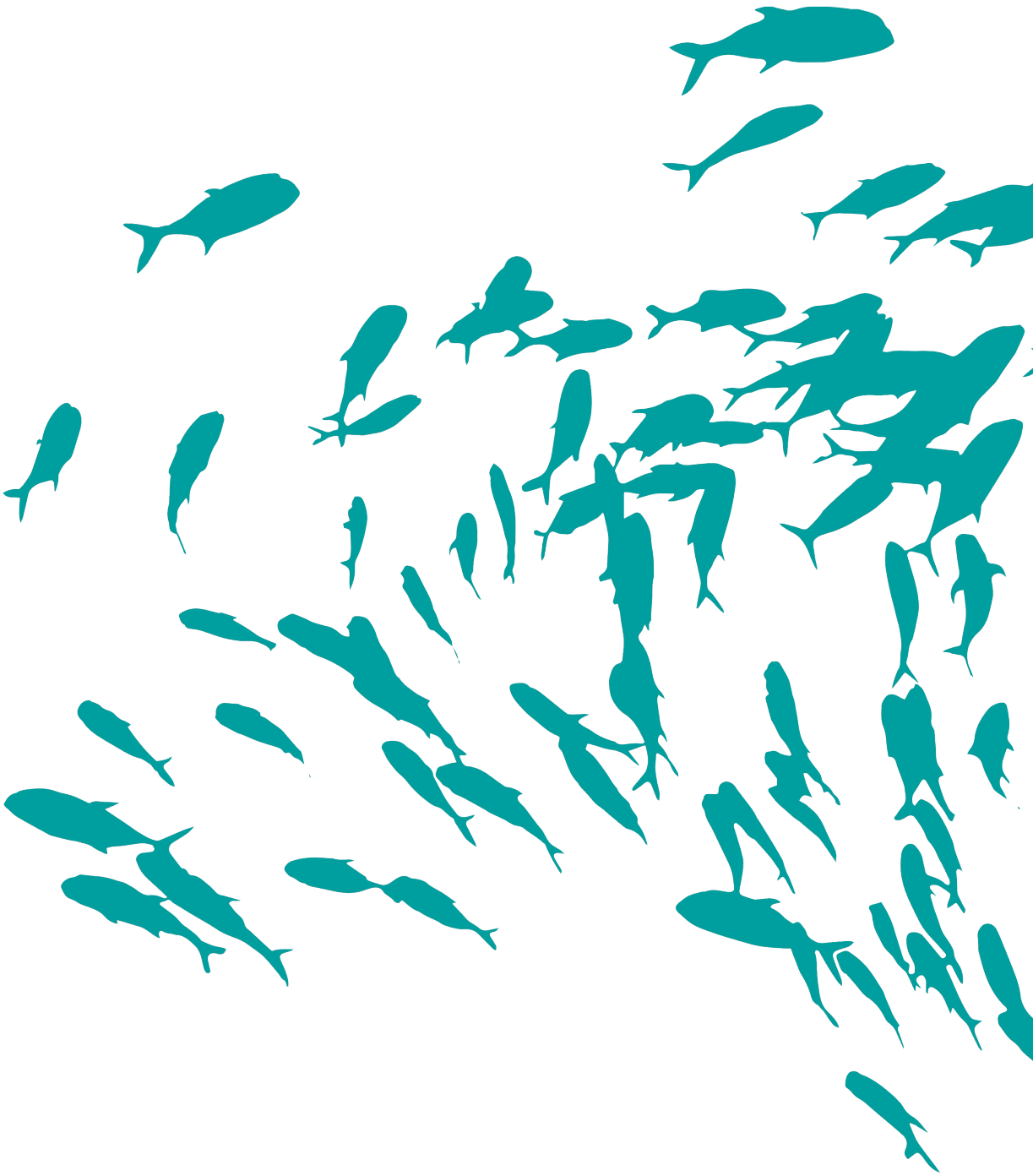
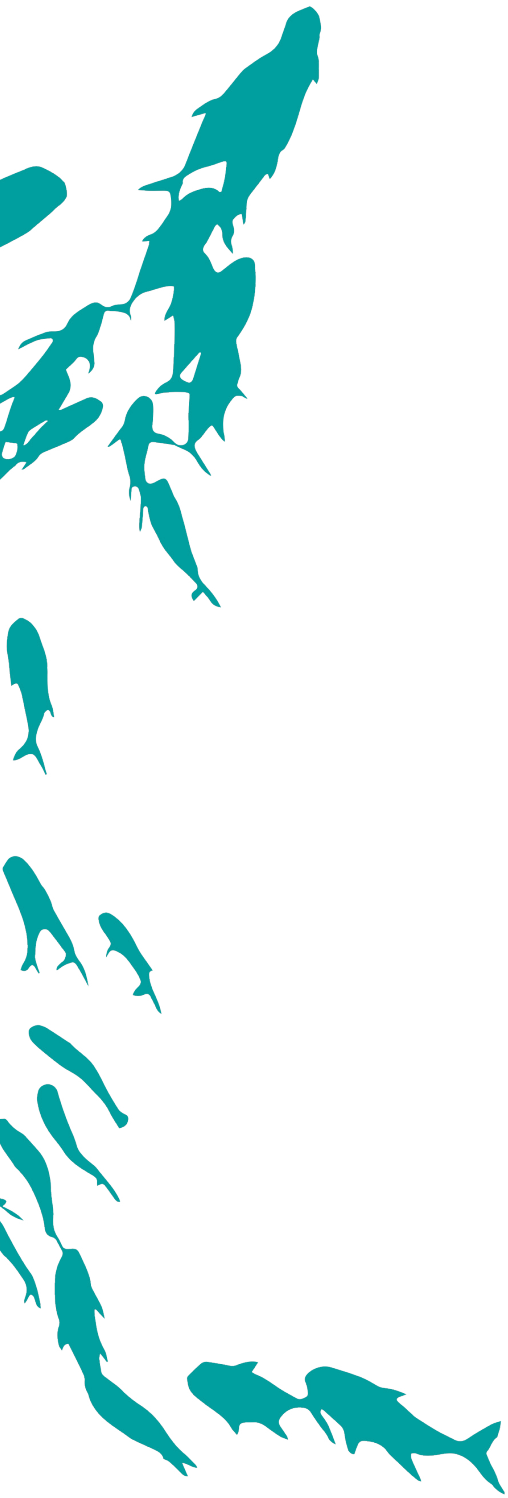




CHAPTER 9

General discussion

The aim of this thesis was to optimize and individualize radiation dose and contrast media (CM) injection protocols in abdominal computed tomography (CT). Image quality is influenced by scanner-related (e.g. tube voltage, tube current, slice reconstruction, scan delay and kernel), CM-related (e.g. CM volume, flow rate, concentration, iodine delivery rate (IDR), viscosity, needle gauge and saline chaser) and patient-related (e.g. weight, body mass index (BMI), blood volume, heart rate, cardiac output and breath hold) parameters (1-15). All of these should be taken into account when performing a CT scan, as they not only affect image quality but also each other. Various parameters were analysed separately to gain better insight into the different aspects of scanner related, CM related and patient related factors, with the ultimate goal being an individualized optimized protocol integrating all pertinent parameters.

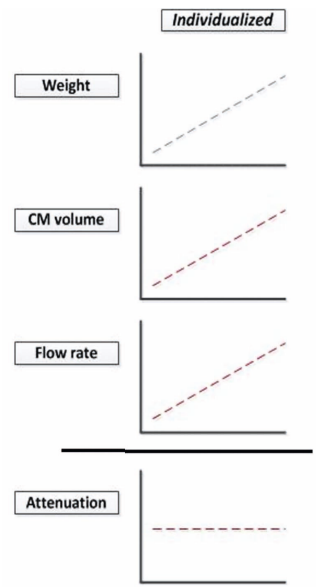
In **chapter 2,** it was shown that an individualized CM injection protocol, adapting both CM volume and flow rate to patient body weight, results in more homogeneous enhancement of liver parenchyma than a standard CM injection protocol (figure 1). Furthermore, a body weight adapted CM injection protocol results in CM volume reduction in a large percentage of the population. This CM reduction was comparable to those achieved in similar studies in the setting of cardiac and pulmonary embolism (9, 12).

Even though total body weight is an easy-to-use approach in clinical practice, previous studies found that lean body weight (LBW) may be more precise. This is because fat contains less blood vessels than other tissue and does not play an important role in CM distribution (16-18).

Furthermore, adapting CM volume to patient body weight is not sufficient for reaching optimal image quality. Tube voltage must be taken into account as well, because as it approaches the 33 keV k-edge of iodine decreasing tube voltage results in increased CM attenuation.

The COMpLEx randomised controlled trial detailed in **Chapter 3** puts this theory into practice. Participants were randomly assigned into four groups according to body weight-adapted CM dosing factor and tube voltage. Group 1 received 0.521 g I/kg CM at a tube voltage of 120 kV (based on the landmark paper by Heiken et al. (2)).

Figure 1. When contrast (CM) volume and flow rate are adapted to patient body weight, weight-dependent attenuation is eliminated. Homogeneous enhancement of the liver parenchyma is achieved without compromising image quality.

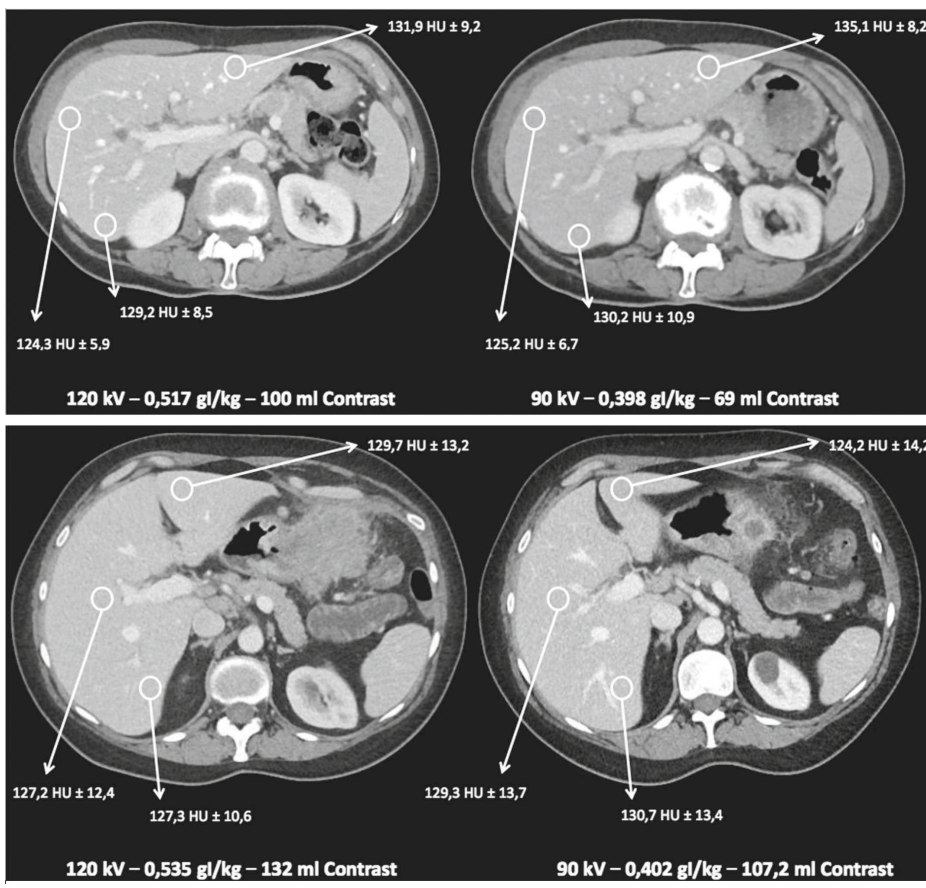


Group 2 received the same CM dosage at a lower tube voltage of 90 kV. Groups 3 and 4 received CM dosages adapted according to the 10-to-10 rule, which pairs a 10 kV reduction in tube voltage with a 10 % decrease in CM dose (based on Canstein and Korporaal (19)). Group 3 was scanned at 100 kV (20 kV reduction compared to Group 1), with 0.417 g I/kg CM (20 % CM reduction), and group 4 was scanned at 90 kV (-30 kV), with 0.365 g I/kg CM (-30 %). The results showed that the proposed 10-to-10 rule is an easily reproducible method for achieving homogeneous enhancement in portal venous CT of the liver throughout the patient population, irrespective of patient body weight or tube voltage. This is illustrated in Figure 2, which shows images of two patients undergoing regular CT scans for oncological follow-up: even though parameters differ between the first and second scans - both tube voltage and contrast volume are reduced by 30% - comparable attenuation of the liver parenchyma is achieved.

Automated tube current modulation (ATCM) and automated tube voltage selection (ATVS) techniques individualize radiation dose based on patient body habitus and the clinical question, but CM injection protocols are still mainly set manually. A connection between scanner and CM injector would enable

automation of the 10-to-10 rule, making it easier to adapt protocols to both tube voltage and patient, decreasing time spent by the technician in setting up the CM protocol, and eventually decreasing costs (e.g. by being able to perform more scans on a daily basis).

Figure 2. Two repeat scans of two oncological follow-up patients (1 and 2).



Repeat scans were done 6-12 months apart using different scan protocols. First scans (A & B) were performed with standard tube voltage of 120 kV and a body weight adapted contrast injection protocol. The second scans (C & D), were performed with a 30 kV tube voltage reduction and a corresponding 30 % decrease in dosing factor, as per the 10-to-10 rule. Enhancement of the liver parenchyma is comparable between scans of the same patient.

Since LBW may be a more reliable than total body weight for CM injection protocol adaptation, it would be interesting to study the performance of the 10-to-10 rule when using LBW.

Image quality is not only influenced by CM injection but also radiation dose protocols. The radiation dose can be decreased by reducing tube voltage (in kV), tube current (in mAs) or both (19, 20). In **chapter 4**, reconstruction software was used to show that a tube current reduction of 10-40 % was possible with iterative reconstruction (IR) strength 4. The highest objective and subjective image quality was achieved with a 10 % mAs reduction, but a 40 % reduction still maintained sufficient image quality. Results were based on pairwise intra-patient comparisons, using raw CT image data to mimic lower tube current scans (by increasing noise) at different IR strengths. In absence of a reliable image quality standard, various objective and subjective image quality parameters were used. For objective image quality, signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) are most often used in the literature to illustrate image quality, but there is no consensus on threshold or cut-off values (21-25). Subjective image quality, as the name implies, is subjective, and while some readers prefer more noise, others may have a preference for a smoother appearance of depicted organs (26). Thus, results on image quality cannot be considered hard outcomes, and illustrate the need for an objective parameter that can be used to reliably and consistently assess image quality in a generalisable way.

Aside from CM dose protocols based on body weight, tube voltage, tube current and IR strength, other patient-related parameters are of importance. In **Chapter 5,** adaptation of either CM dose or radiation dose, depending on patient's age and renal function, is investigated. Because tube voltage is dependent not only on the clinical question and a user set CNR but also on patient body composition, a higher tube voltage is used in heavier patients and a lower tube voltage in leaner patients to reach the same CNR. However, CNR is also affected by the amount of CM used. Thus, a similar CNR could be achieved by simultaneously decreasing radiation dose and increasing CM dose, or vice versa. This can be achieved using image-task-dependent optimisation settings (slider levels) (32): position 11 leads to an increase in noise (-26 % radiation dose) and an increase in CM dose (+26 % volume), and in position 3 noise is low and CNR is based solely on the fat-water contrast(27). This protocol can be used to achieve a -16 % reduction in CM dose, at the cost of a 37 % increase in radiation dose to generate the same CNR.

The study detailed in Chapter 5 evaluates the above in 6 Gottingen minipigs. The pigs were scanned in early arterial, portal venous and delayed phase with three different scan and CM injection protocols. The standard protocol was a slider position 7 and CM dose of 0.350 gI/kg, CM dose saving was slider position 3 with 0.294 gI/kg, and position 11 was used for radiation dose saving, with an increase in CM volume to 0.441 gI/kg. Results showed no significant differences between groups regarding SNR, CNR and subjective image quality. Only noise was rated significantly higher in the radiation dose saving group. These results are promising for including age and kidney function in further individualisation of scan and CM injection protocols.

One other factor must be considered for a complete picture of image quality and optimalization of protocols: patient comfort. Not only is this important to the patient in question, but an uncomfortable patient will also affect image quality by physiological stress reactions and the inability to be still. Furthermore, such a patient may be afraid to come back, further increasing interference every repeat scan. Such factors may ruin the timing of both scan and CM injection protocol, not to mention planned schedules. In **Chapter 6** the effect of pre-warming CM on patient comfort and pain is evaluated. CM was injected either at room temperature (~23°C [~73°F]) or pre-warmed to body temperature (37°C [99°F]). Results showed that iodinated CM at room temperature was not inferior to pre-warmed CM in patient comfort in abdominal CT imaging. Furthermore, pre-warming CM did not lead to an increase in image quality, safety and/or patient comfort. The flow rate in the study was low, but in our hospital more than 90 % of scans performed between 2013 and 2019 were done with a similar flow rate (<6 ml/s). Regarding optimization and individualization of radiation and CM protocols, pre-warming CM might therefore no longer be a pre-requisite in standard state-of-the art abdominal injection protocols in daily clinical routine.

Chapter 7 combines the most important protocol individualization aspects in both vascular and parenchymal studies, including the 10-to-10 rule, based on various studies performed by our group over the last years (6, 7, 9-13, 15). IDR is considered the most decisive factor of the CM injection protocol in vascular studies, but in parenchymal studies total CM volume is leading (1). Therefore, in vascular studies a tube voltage reduction of 10 kV should be followed by a

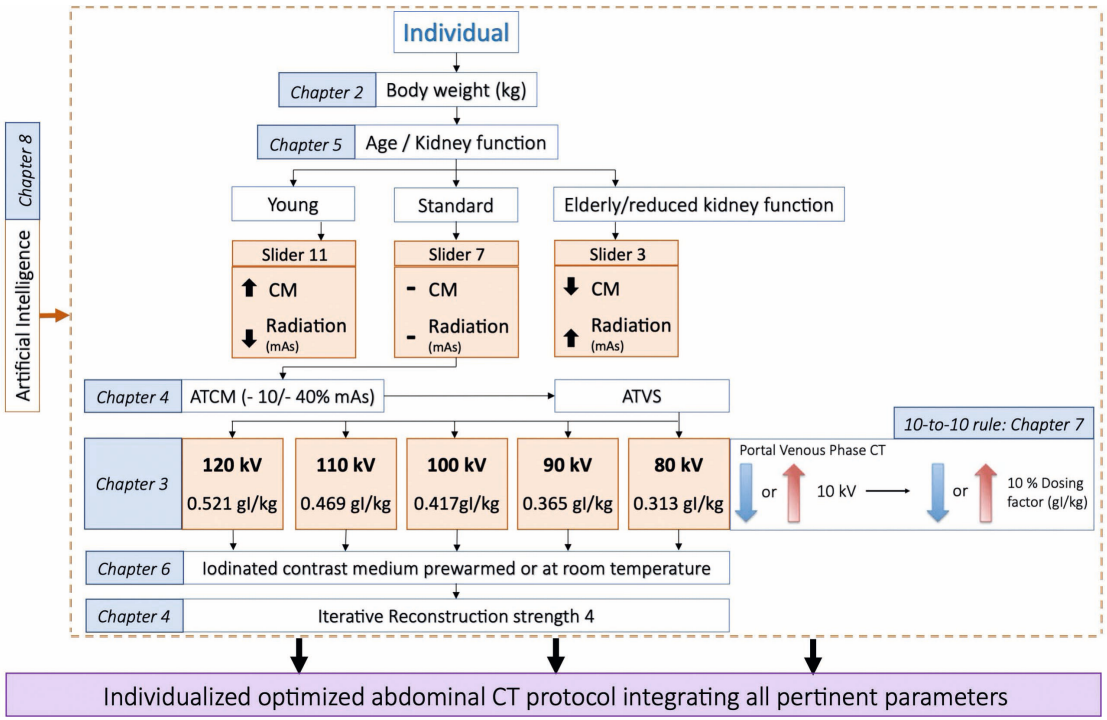
10 % decrease in IDR, whereas in abdominal imaging a 10 kV reduction should be accompanied by a 10 % decrease in dosing factor (in g I/s).

Figure 3 provides an overview of how to reach individualized optimized scan and CM injection protocols in abdominal imaging, integrating all pertinent parameters evaluated in this thesis. The process starts with the patient. Ideally the patients' body weight is measured on a calibrated weighing scale available in the scanner room. The measured body weight is used to individualize the CM injection protocol. Subsequently, the slider position is chosen based on the age of the patient and/or kidney function. ATCM and ATVS techniques are used to individualize the radiation dose to the individual patient body habitus. Based on the 10-to-10 rule the CM injection protocol is adapted to both body weight and the ATVS selected tube voltage. Contrast material can be injected at either room temperature or pre-warmed, without negatively influencing image quality, safety, or patient comfort. By reconstructing images with IR strength 4, a tube current reduction of 10 – 40 % can be reached, resulting in excellent to sufficient image quality. When taken separately, these different facets may appear quite manageable and clear, but when put together they may become confusing and difficult to handle. The combined theory may be considered utopia for daily clinical practice if one expects technicians to take into account all the different parameters and their interactions. Furthermore, too many influencing parameters makes the individualized and optimized scan protocol prone to error. AI might be necessary to make it workable. **Chapter 8** inspects how AI could determine individualized CM, scan and reconstruction parameters for each patient. The focus lies on cardiac imaging, but suggestions are widely applicable to other areas including abdominal imaging.

Future directions

The studies in the present thesis were all performed in the same hospital. As a consequence CM types and concentrations as well as scanner vendors between studies were similar. This limits generalizability of the results. Different vendors use different techniques for optimizing image quality (4). The preferred IR strength and the possible accompanying tube current reduction is vendor specific.

Figure 3. Overview of this thesis: custom-made computed tomography of the abdomen.



Customisation starts when a patient enters the scanner room. Body weight is ideally measured on a calibrated weighing scale to enable individualisation of the contrast media (CM) injection protocol, after which the slider position is chosen, depending on patient age and/or kidney function (a tube current reduction up to 40 % can be achieved by using iterative reconstruction [IR] strength 4). Automated tube current modulation (ATCM) and automated tube voltage selection (ATVS) techniques enable the scanner to automatically determine optimal tube voltage based on patient characteristics. Finally, CM volume is adapted to both patient body weight and the tube voltage used, bearing in mind the 10-to-10 rule. In this setting, iodinated CM can be administered either pre-warmed or at room temperature. Artificial intelligence might be able to facilitate this customisation process in the future.

However, chapter 4 provides information on how to find optimal IR strength and tube current in each center, the method is again vendor dependent. Not all vendors make the raw data available, which is required for the use of reconstruction software. Furthermore, image-task-dependent optimisation settings (slider levels) are only available on scanners of a specific vendor type. By contrast the 10-to-10 rule is expected to be robust, as the physical effect of the 33 keV edge of iodine is similar in all cases. Increasing CM iodine concentration increases its viscosity, limiting generalisability of the results of the CATCHY trial. It can only be stated that injecting CM with 300 mg iodine per ml at room temperature or pre-warmed led to comparable image quality, safety and patient comfort. These examples show the main limitations of the present thesis. Preferably, the combined results need to be evaluated in a large multi-center trial, taking into account the whole range of CM types and concentrations as well as vendors.

Future research could focus on a variety of related themes. Most importantly, a universal objective image quality parameter, able to capture all the different pertinent aspects, should be developed. The want of such a parameter is a common thread throughout the studies of this thesis. Collaboration between clinical physicists and radiologists is essential here, and AI might be helpful in objectifying aspects of image quality.

Another important aspect to study is which body size parameter is most reliable for CM protocol individualisation. This has been done in the Chinese population, and LBW appears to be most promising (16, 17, 28). Recently De Jong et al. used an AI algorithm to calculate patient LBW and based CM protocols on weight categories in Dutch patients: they found liver enhancement to be most strongly associated with LBW compared to total body weight or BMI (18). Even though these consistent results are encouraging, large prospective studies in more diverse populations are necessary for firm conclusions to be drawn.

As present thesis shows, many of the aspects in individualizing radiation and CM injection protocols have been investigated in CT imaging. However, in magnetic resonance imaging (MRI) patients are still more likely to receive a one-size-fits all protocol, or a protocol based on weight categories. This offers a whole range of new research opportunities.

The CATCHY trial found little effect of CM temperature on patient comfort. However, CM flow rate in the trial was relatively low (< 6 ml/s). It would be interesting to evaluate the effect of CM temperature at higher flow rates. Previous studies report increased rates of adverse events when certain types of CM are not pre-warmed, and guidelines on safe use of contrast material assume pre-warming CM will be helpful to minimize complications (7, 33-35, 37, 38). To the best of our knowledge, there is no logical explanation for such an assumption. The largest study on the subject - a retrospective analysis of 24 830 power-injections - found no effect of pre-warming for iopamidol 300 but a tripling of adverse events for 20°C iopamidol 370 (36). The authors concluded that pre-warming may be beneficial in more viscous CM. However, the patient comfort or mild adverse events were not included in the study, and room temperatures may be higher than 20 degrees in clinical practice. During the CATCHY trial room temperature CM was 23°C on average. Finally, both studies kept the flow rates relatively low, < 6 ml/s. A large study comparing adverse event rates and patient comfort at a wide range of flow rates and different CM concentrations and with clinical practice reflecting temperatures may finally provide a definite answer as to the utility of CM pre-warming.

AI is an emerging field in daily clinical practice and might be helpful in individualizing both radiation and CM injection protocols. An AI driven automatic attenuation check of the targeted structure could be next, followed by automated pathology detection coupled with a warning signal in case of acute pathology in need of immediate attention. Once a reliable, general and consequent objective image quality parameter has been developed, AI algorithms could be able to determine which parameters to adjust in cases of insufficient image quality, avoiding non-diagnostic scans altogether.

Conclusion

The present thesis provides an overview of how different parameters can be adjusted to individualize and optimize radiation and CM injection protocols. Not only body weight and tube voltage are of the essence. Tube current, patient comfort and age considerations may also contribute toward ideal image quality for each patient, every time. Future research may focus on involving AI in this process, to facilitate optimal integration of all the different facets and perhaps even generate a result that is greater than the sum of its parts.

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CHAPTER 10

Summary
Nederlandse samenvatting

Since the invention of the computed tomography (CT) scanner in 1971, contrast media (CM) injection protocols, software, and scanners have rapidly evolved. In the beginning, a one-size-fits all scan protocol was applied: administered radiation and CM doses were similar for each patient. However, as scanners evolved it became possible to use different tube current and tube voltage settings based on individual body composition. Automated tube current modulation (ATCM) and automated tube voltage selection (ATVS) techniques optimize radiation dose based on patient characteristics as well as a user set image quality. Previous studies showed that in vascular studies the CM injection protocol is mainly determined by the iodine delivery rate (IDR), while in parenchymal studies total CM volume is most decisive. A decrease in tube voltage will reduce radiation dose, but due to the 33 keV-edge of iodine it will also result in increased attenuation. Therefore, a reduction in tube voltage is advantageous for both radiation and CM dose. The downside of decreasing tube voltage is an increase in image noise, which is why radiologists must work with the delicate balance reflected in the "as low as reasonably achievable" (ALARA) principle. The aim of the present thesis was to investigate this balance so as to provide guidance for individualisation of both radiation and CM dose, based on the clinical question and patient characteristics, and to obtain optimal image quality in each patient, every time.

In **chapter 2** a body weight adapted CM injection protocol in abdominal imaging is introduced. As has previously been shown in cardiac and pulmonary artery imaging, an individualized protocol based on body weight results in a more homogeneous enhancement of the target structure (the liver), compared to a one-size-fits all protocol.

The hypothesis of **chapter 3** was that a body weight-based CM injection protocol adapted to the tube voltage used would result in homogeneous enhancement of the liver parenchyma across patients. In this double-blinded randomized controlled trial, 256 patients were randomly assigned to one of the four groups. In group 1, the reference group, the presumed gold standard scanning and CM protocols were used: 120 kV and 0.521 g I/kg. In group 2, the tube voltage was reduced to 90 kV, but CM administration was maintained as for group 1. In group 3, the tube voltage was reduced to 100 kV, i.e., 20 kV less than group 1, and CM was reduced by a corresponding 20 % to 0.417 g I/

kg. Group 4 received a 90 kV scan protocol (-30 kV), and a corresponding CM reduction to 0.365 g I/kg (-30 %). The results confirmed the hypothesis: the weight and tube voltage-based CM injection protocols used in groups 1, 3 and 4 led to homogeneous enhancement of the liver across patients in portal venous phase abdominal imaging.

In **chapter 4** the optimal iterative reconstruction (IR) strength and tube current for abdominal imaging are investigated using reconstruction software. Pairwise intra-patient comparisons showed that IR strength 4 led to the best subjective image quality, while a 10 to 40 % reduction in tube current was possible without compromising the objective and subjective image quality.

In the previous chapters, optimisation according to body weight, tube voltage, tube current and IR strength were investigated. In **chapter 5** the parameters age, kidney function and the need for repetitive scanning (as in oncological follow-up for example) were explored. These patient characteristics determine whether the risk of CM or radiation are most relevant. Because ATVS choses a particular tube voltage based on a desired contrast-to-noise ratio (CNR), and because CNR is determined by both contrast and radiation dose, decreasing one and increasing the other – or vice versa – will maintain a constant CNR. In an experimental set up with 6 Göttingen minipigs optimizing either radiation (-26 %) or CM dose (-16 %) led to comparable objective and subjective image quality. The results suggest that it is feasible to optimize either the radiation or the CM dose based on individual risk assessment.

Chapter 6 details a prospective study in 218 patients to evaluate whether administering CM at room temperature resulted in comparable image quality, safety and participant comfort compared to pre-warmed CM administration (37° C [99° F]) in abdominal CT imaging. In contrast to the European guideline, which states that pre-warming CM improves patient comfort and reduces the number of adverse events, the present study showed that applying CM at room temperature is noninferior with respect to image quality, safety and comfort in this setting.

The editorial in **chapter 7**, outlines the 10-to-10 rule. This rule states that a 10 kV reduction in tube voltage should result in a 10 % decrease in IDR in vascular

studies and a 10 % decrease in dosing factor (in g I/kg) in parenchymal studies, and vice versa. Both statements have been prospectively verified in previous trials by our group, and one is included in this thesis (chapter 3).

In short, the present thesis proposes several parameters to base scan and CM injection protocols on in abdominal CT imaging. It may not be easy to incorporate all these different facets within an efficient workflow, but artificial intelligence (AI) may provide a solution. **Chapter 8** discusses the possibilities of AI in cardiac imaging. The chapter focuses mainly on CT angiography, but the large majority of suggestions are most likely applicable to parenchymal imaging. For example, AI could provide an automatic attenuation check, followed by pathology detection. When enhancement of the targeted structure is found to be insufficient, improved scan and CM protocols could be automatically proposed. As for the pathology check, a warning signal could be generated whenever an acute pathology is detected. Thus AI may be helpful on different levels to improve daily clinical workflow efficiency.

Nederlandse Samenvatting

Sinds de ontdekking van de CT-scanner in 1971 zijn de contrast media (CM) protocollen, software en de scanners zelf snel ontwikkeld. In het begin werd er een *one-size-fits all* methode gebruikt. De stralingsdosis was gelijk in iedere patiënt, net als de hoeveelheid CM die werd toegediend. Echter, door de technische ontwikkeling van de scanner, werd het mogelijk om scans te verrichten met een verschillende buisstroom (mAs) en buisspanning (kV). *Automated tube current modulation* (ATCM) en *automated tube voltage selection* (ATVS) technieken optimaliseren de stralingsdosis gebaseerd op een beeldkwaliteit die vooraf door de gebruiker is vastgesteld, als ook op de individuele patiënt karakteristieken. Eerdere studies hebben daarnaast aangetoond dat voor de optimalisatie van CM protocollen in vasculaire studies de *iodine delivery rate* (IDR) de meest belangrijke factor is, terwijl voor parenchymateuze studies het totale CM volume het meest essentieel is. Vanwege de 33 keV-*edge* van jodium, is het zo dat een daling in het kV – waarbij de totale stralingsdosis wordt verlaagd – resulteert in een toename in de aankleuring van het jodium. Een verlaging van de buisspanning kan dus een voordeel zijn voor zowel de stralingsdosis als het CM volume. Het nadeel van het verlagen van de buisspanning is echter een toename in ruis. Dit toont het fragiele evenwicht van het "*as low as reasonably achievable"* (ALARA) principe. Het doel van de huidige thesis is om deze balans verder uit te diepen en te onderzoeken hoe zowel de straling als CM dosis geïndividualiseerd kan worden, gebaseerd op zowel de klinische vraag als de patiënt karakteristieken. Met hierbij als doel een optimale beeldkwaliteit te behalen in iedere patiënt, elke keer.

In **hoofdstuk 2** wordt een CM injectie protocol aangepast aan het lichaamsgewicht van de patiënt in abdominale CT geïntroduceerd. Zoals eerder aangetoond in beeldvorming van het hart en de pulmonaal arteriën, resulteert een CM protocol gebaseerd op lichaamsgewicht in meer homogene aankleuring van het doelorgaan in vergelijking met een *one-size-fits all* protocol. Tegelijkertijd wordt in deze eerdere studies een vermindering in de totale hoeveelheid CM behaald in een groot deel van de populatie. Resultaten van dit hoofdstuk zijn in lijn met deze eerdere studies: Een CM protocol gebaseerd op lichaamsgewicht resulteert in een homogene aankleuring van de lever, in vergelijking met een protocol waarbij iedere patiënt dezelfde hoeveelheid CM heeft gekregen.

De hypothese voor **hoofdstuk 3** was dat een CM injectie protocol gebaseerd op lichaamsgewicht, aangepast aan de buisspanning, resulteert in homogene aankleuring van het lever parenchym tussen patiënten. In deze dubbelblinde, gerandomiseerde studie werden 256 geïncludeerd in een van de vier groepen. In groep 1 werd er gescand met de 'gouden standaard': 120 kV en een CM protocol aangepast aan het lichaamsgewicht van 0.521 g I/kg. In groep 2 werd de buisspanning verlaagd naar 90 kV, terwijl het CM protocol identiek bleef aan dat gebruikt in groep 1. In groep 3 werd de buisspanning verlaagd naar 100 kV en daarom werd het contrast ook verlaagd met 20 % (in vergelijking met groep 1) tot 0.417 g I/kg. In groep 4 werden patiënten gescand met 90 kV en 0.365 g I/kg (een reductie van 30 %). De hypothese werd bevestigd dat een CM injectie protocol gebaseerd op lichaamsgewicht en de gebruikte buisspanning leidde tot homogene aankleuring van de lever in abdominale CT in portaal veneuze fase.

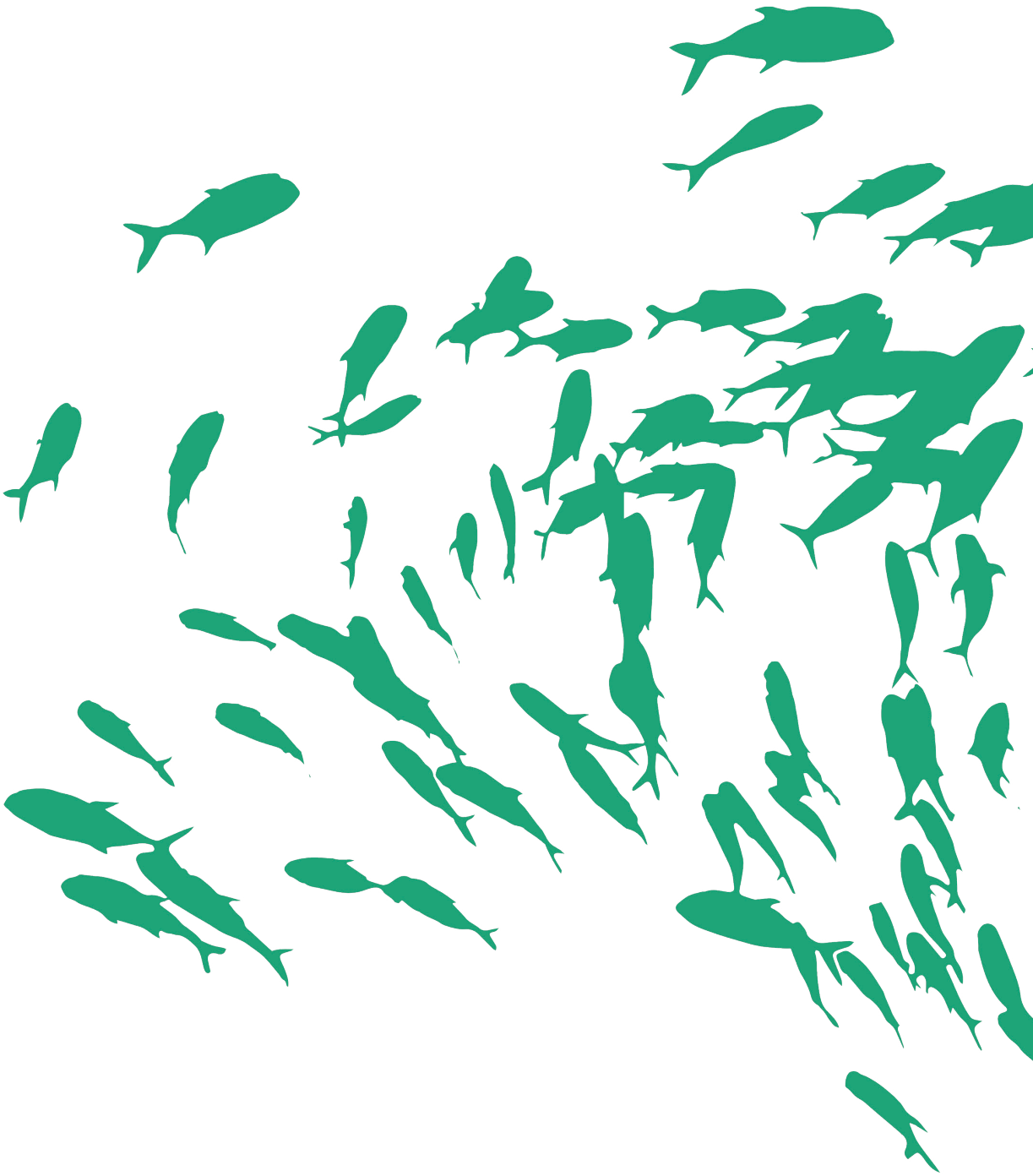
Hoofdstuk 4 onderzocht de optimale iteratieve reconstructie (IR) sterkte en buisstroom in abdominale CT met het gebruik van reconstructie software. Deze studie toonde door paarsgewijze vergelijking in dezelfde patiënt aan dat IR-sterkte 4 de beste subjectieve beeldkwaliteit gaf, terwijl een 10 – 40 % verlaging in de buisstroom mogelijk was zonder afbreuk te doen aan de objectieve en subjectieve beeldkwaliteit.

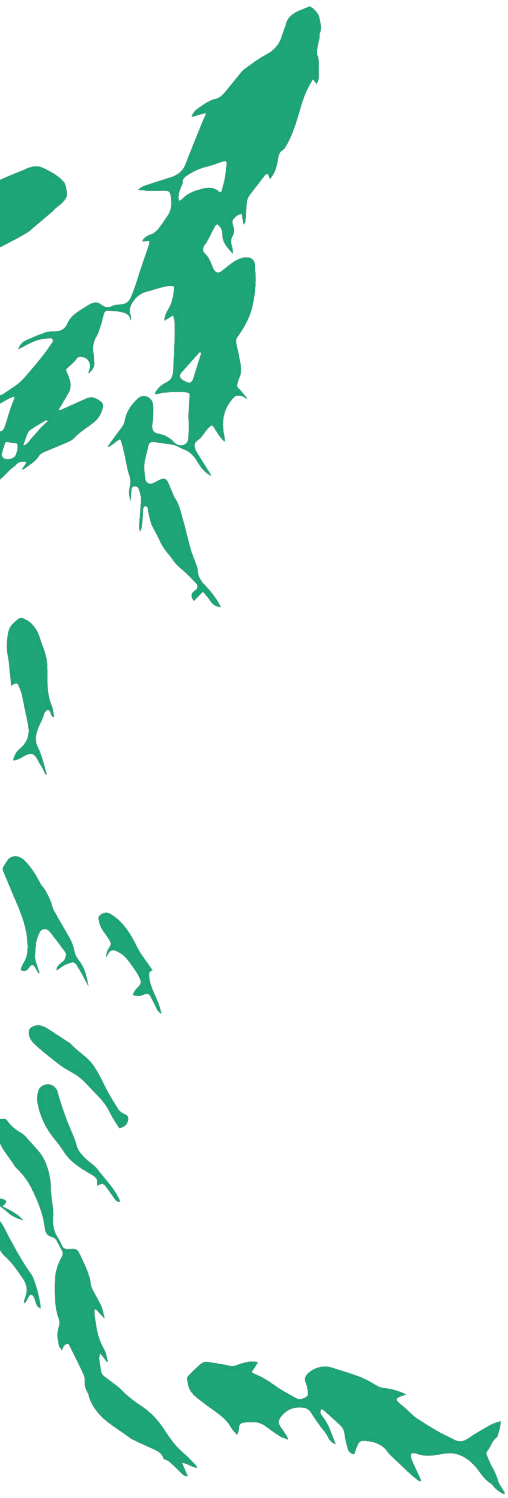
Lichaamsgewicht, buisspanning, buisstroom en IR sterkte werden onderzocht in de voorgaande hoofdstukken. In **hoofdstuk 5** werden de parameters leeftijd, nierfunctie en de noodzaak om een patiënt herhaaldelijk te scannen (e.g. oncologische follow-up) meegenomen als factoren om het CM protocol op te baseren. ATVS kiest een bepaalde buisspanning, gebaseerd op een gewenste *contrast-to-noise ratio* (CNR). Echter, de CNR wordt bepaald door zowel het contrast als de stralingsdosis. Door de een te verlagen en de ander te verhogen – of omgekeerd – kan de CNR constant worden gehouden. In een experimentele opzet in 6 *Göttingen* mini-varkentjes leidde het optimaliseren van enkel de stralingsdosis (-26 %) of de CM dosis (-16 %) tot een vergelijkbare objectieve en subjectieve beeldkwaliteit. Daarom kan redelijkerwijs worden aangenomen dat het mogelijk is enkel de stralings- of de CM dosis te optimaliseren, afhankelijk van een individuele risicobepaling.

Hoofdstuk 6 onderzocht prospectief in 218 patiënten of het toedienen van CM op kamertemperatuur resulteerde in vergelijkbare beeldkwaliteit, veiligheid en patiënt comfort ten opzichte van verwarmd CM (37° C [99° F]) in abdominale CT. In tegenstelling tot de Europese richtlijn, die stelt dat CM verwarming de patiënt meer comfortabel maakt en de kans op ongewenste voorvallen verminderd, toont de huidige studie dat CM op kamertemperatuur non-inferieur was met betrekking tot beeldkwaliteit, veiligheid en comfort.

In **hoofdstuk 7** wordt de 10-tot-10 regel samengevat in een *editorial*. Deze regelt stelt dat een 10 kV verlaging in buisspanning zou moeten leiden tot een 10 % vermindering in IDR voor vasculaire studies en 10 % verlaging van het aantal g I/kg in CT's van de parenchymateuze organen en omgekeerd. Beide statements zijn prospectief onderbouwd in eerdere studies verricht door onze groep of gepresenteerd in de huidige thesis.

Deze thesis zet verschillende parameters uiteen waarop het scan en CM injectie protocol in abdominale CT gebaseerd kan worden. Om al deze verschillende facetten te integreren en tegelijkertijd de *workflow* efficiënt te houden, zou artificiële intelligentie (AI) een oplossing kunnen zijn. **Hoofdstuk 8** bediscussieert de verschillende mogelijkheden van AI in cardiale beeldvorming. Alhoewel gericht op het hart, zouden deze suggesties ook van toepassing kunnen zijn op de abdominale beeldvorming. AI zou bijvoorbeeld kunnen zorgen voor een automatische aankleurings-check, gevolgd door de detectie van eventueel aanwezige acute pathologie. In het geval van onvoldoende aankleuring van het doelorgaan kan AI een verbeterd scan en CM protocol voorstellen en de patiënt opnieuw laten scannen, voordat deze terug gaat naar huis. Met betrekking tot de pathologiecontrole kan een waarschuwingssignaal afgaan bij de aanwezigheid van acute pathologie. Door AI te introduceren zou op deze manier de dagelijkse klinische *workflow* efficiënter kunnen worden.





CHAPTER 11

Scientific impact

11.1 Research

Radiation dose and contrast media (CM) together ensure image quality in (abdominal) computed tomography (CT) imaging. However, using a one size fits all protocol may not be the best tactic. Optimizing radiation and CM dose will result in individualized scan and CM protocols in which, ideally, each patient will receive the optimal amount of both to reach diagnostic image quality. In such optimization, however, the type of CT study performed must be taken into account. In vascular studies the iodine delivery rate (IDR, in gI/s) is considered the most decisive factor. For parenchymal studies, the CM volume (in ml) is the most important parameter to reach optimal enhancement of the target organ (1). The aim of the current thesis was to find the optimal radiation and CM dose for each patient in abdominal imaging. This thesis proposes a 10-to-10 rule of thumb to individualize scan and CM injection protocols. A 10 kV decrease in tube voltage should be accompanied by a 10 % decrease in IDR for vascular studies and a 10 % decrease in dosing factor for a parenchymal CT, and vice versa. Results of a randomized controlled trial (COMpLEx trial) confirmed this easy to implement rule of thumb in abdominal imaging.

To date a disagreement exists between the European and American guidelines regarding the necessity to pre-warm CM to body temperature before intravenous administration (2, 3). The current thesis provides high level evidence that pre-warming CM does not result in increased image quality, safety, or patient comfort in abdominal CT imaging (CATCHY trial). This result could improve work flow efficiency in daily clinical practice, as there may be no need to store CM in a warming cabinet.

Apart from body weight, tube voltage and CM temperature, this thesis proposes to add the patient characteristics age and kidney function to the parameters used for protocol optimization. In younger patients and patients in need of frequent scanning, radiation dose reduction is preferred, whereas patients with reduced kidney function (more frequently seen in the elderly population) may benefit more from CM dose reduction. These additional patient characteristics were evaluated in an animal feasibility study with promising results.

The present thesis tackles different parameters step by step. However, combining all pertinent factors into one protocol is challenging. Artificial intelligence (AI) could be the solution to further optimize daily workflow in the CT department. AI could for example, aid in radiation and CM protocol individualization, detect insufficient image quality at an early stage, and provide a warning signal upon the detection of an acute pathology requiring immediate viewing by a radiologist.

11.2 Relevance

In the past, a one-size fits all protocol was used for both radiation – tube voltage and tube current – and CM dose protocols. However, rapid technical developments made it possible to adapt tube current and tube voltage to the clinical question and patient body weight, substantially reducing radiation dose (4). In daily clinical routine worldwide, CM is still often administered in a one-size-fits all fashion. Previous studies from our group and of the present thesis show that individualizing the CM protocol based on body weight results in more homogeneous enhancement in cardiac, pulmonary artery, and abdominal imaging. Furthermore, a simultaneous reduction in total injected CM volume was achieved in a large percentage of the population (5, 6).

Radiation and CM dose are often treated as two separate entities. However, considering both parameters in conjunction opens new doors. The 10-to-10 rule offers an easy-to-use and readily implemented rule of thumb to adapt both parameters to one another. By introducing an opportunity to adapt either the radiation or the CM dose – depending on age, kidney function or the necessity for repetitive scanning – protocols can be further optimized based on individual risk assessment.

The present thesis provides a manual on how to individualize CT protocols in daily clinical practice. By applying the proposed rules, it is possible to reach sufficient image quality in each patient, every time, whilst maintaining the perfect balance between radiation and CM dose.

11.3 Target groups

There are four groups for which this thesis could be relevant.

1. Radiologists

Radiologists in general are aware of the fact that radiation and CM protocols influence image quality. However, there is too little awareness of how protocols influence important aspects such as lesion characterization. Different protocols – between hospitals, scanners, and moments in time – will result in different attenuation levels. In kidney lesions for example, attenuation predicts the likelihood of a malignant lesion. Therefore, homogeneity between and within patients is desirable in order to draw reliable conclusions from each scan. The current thesis provides an easy-to-use rule of thumb to reach such homogeneous enhancement in both vascular and abdominal CT imaging.

2. Radiologic Technologists

In the Netherlands, technicians are responsible for acquiring the scan according to protocols as determined by the radiologist. The information in the present thesis may give technician's more insight into why and how protocols are optimized. Furthermore, the suggestions made with regard to the introduction of AI may simplify their job.

3. Referring physicians

Clinicians are happy with a performed CT scan when it is easy to assess and has diagnostic image quality. In order to make sure that we can provide that 'pretty' CT scan, clinicians have to provide a scan indication, clinical background, and correct patient body weight and kidney function. While the current thesis may be too focused on the technical aspects of CT to capture the clinicians' imagination, a little glimpse into the world of the CT department would help them understand why these particular questions are asked of them.

4. The patient

Providing the patient with a CT scan with the highest achievable image quality, assists in diagnosing a diversity of diseases. In addition, decreasing radiation and CM dose diminishes the associated life time attributable cancer risk and possible drop in renal function. Last but not least, comfort is important to the patient. This is reflected in the fact that it was quite easy to find patients willing to participate in the CATCHY trial.

11.4 Activity

Most patients are somewhat familiar with X-ray imaging, but CT and Magnetic Resonance Imaging (MRI) are often confused with one another. In addition, most people do not really know what the work of a radiologist entails. At a first glance this shouldn't be a problem, but it may be beneficial for both referring physician and patient to know a little more about radiology. Referring physicians are informed through presentations. Patients may be reached through social media. Creating awareness of what is done in the CT department to reach diagnostic image quality may improve patients' understanding of procedures, and perhaps even the existence of waiting lists.

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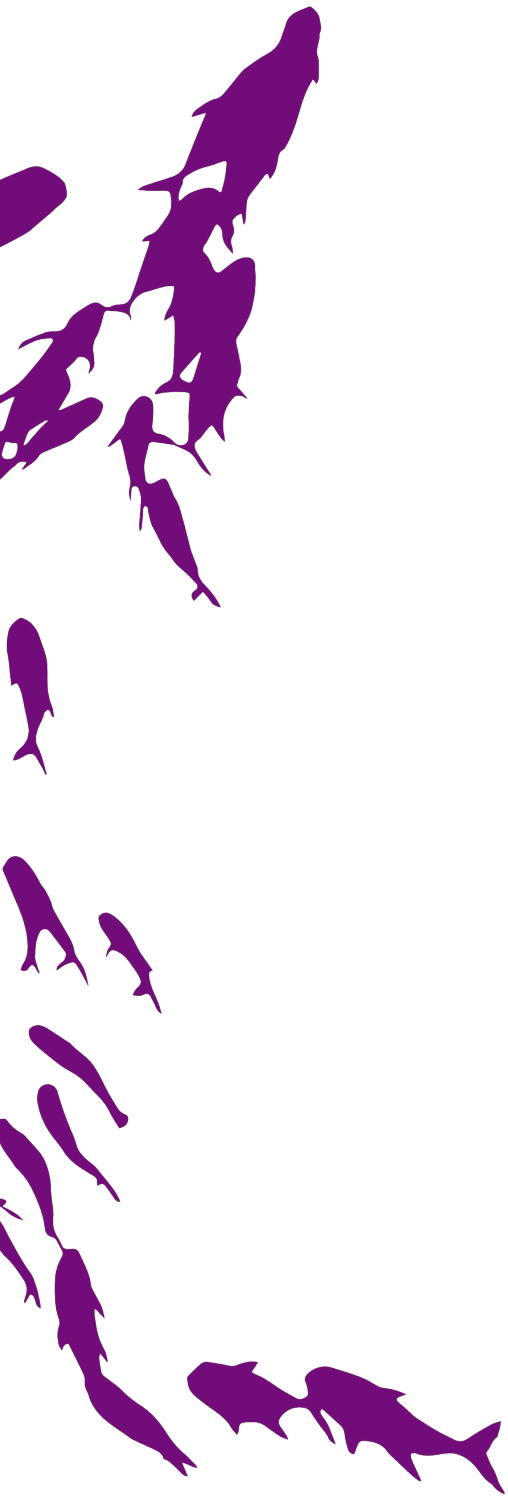

CHAPTER 12

Dankwoord
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Als 'materiaal en methoden' goed in elkaar zitten, dan leidt dit vanzelf tot een goede studie. Deze stelling is wat mij betreft van toepassing op de gehele totstandkoming van dit boekje, zonder een solide basis (onderzoeksteam, afdeling beeldvorming, familie en vrienden) had deze thesis niet tot stand kunnen komen en zeker niet tot het plezier geleid dat ik er nu aan heb gehad. Graag zou ik een aantal personen in het bijzonder willen bedanken:

Prof. Dr. J.E. Wildberger, beste Joachim, uren hebben we samen zitten brainstormen over de opzet van de verschillende studies. Dan was ik overtuigd van een bepaalde richting, maar kon je het plan met één kritische vraag onderuithalen, uiteindelijk leidend tot een proefschrift waarbij geen moment is verspeeld. Ik wil je enorm bedanken voor de tijd die je in je drukke agenda hebt vrijgemaakt om mij te begeleiden, voor je interesse ook in mij als persoon en voor alle mooie kansen en de prettige samenwerking, waar ik veel van heb geleerd en hopelijk nog lang van mag blijven leren.

Dr. C. Mihl, beste Casper, onze eerste kennismaking was, zoals ik me kan herinneren, op jouw verjaardagsfeest in het Forum, waarop je een gele eendjes onesie droeg en waar ik via verschillende wederzijdse vrienden mee naartoe werd gesleurd als AIOS in spe. Wat mij betreft een vrij typerend beeld voor onze latere samenwerking. Je bent altijd beschikbaar, geeft bizar snelle, to-the-point, eerlijke feedback en dat alles met een grote glimlach. Daarnaast wil ik je bedanken voor al je connecties waar ik op mee heb kunnen liften. Ik had me geen prettigere samenwerking kunnen wensen en hoop dat we hier nog lang mee door kunnen gaan. We hebben een biertje verdiend!

Dr. E.C. Nijssen, beste Estelle, een aantal papers was zeker niet zo gemakkelijk gepubliceerd geweest als ze niet eerst door de Estelle-check waren geweest. Bewonderenswaardig hoe je de goede vragen kunt stellen over een onderwerp wat niet echt dicht bij dat van jezelf ligt. Je kritische feedback, met altijd een vriendelijke noot zijn super leerzaam geweest en ik hoop in de toekomst nog vaker van je expertise gebruik te mogen maken.

Babs, bedankt dat je mijn research-buddy, mijn vraagbaak om voor de zoveelste keer uit te leggen hoe (onder andere) een 'collimator' ook alweer werkt en mijn afgetrainde body-double (hoe vaak zijn we niet door elkaar gehaald!?) bent, voor

gezelligheid op feestjes, borrels en congressen zorgt en altijd in bent voor een cappuccino. Samen een fantoom opschuren tot er barstjes in komen, je vent uitlenen voor een extra Engelse check, gesandwiched in de scanner voor een promotiefilmpje, party-en op festivals en als kers op de taart ben je een van mijn paranimfen. Dat we nog maar lang veel plezier mogen beleven!

Nienke, speciaal voor jou een prominent plaatsje in dit dankwoord. Je hebt me enorm op weg geholpen in de struggles van het onderzoek: hoe te beginnen, wie en wat moet ik waar vinden, harde schijven, kluisjes-sleutels, PhD tracks en de eerste opzet van een artikel. Daarnaast moet ik tegelijkertijd met jou Youtube bedanken. Door jou heb ik geleerd dat dit een onmisbare bron is voor 'waterdichte' statistiek!

Lieve CT-laboranten, ik hoop dat jullie beseffen dat dit boekje er zonder jullie hulp niet was geweest. Als ik weer over een nieuwe studie kwam vertellen zag ik jullie soms wat moeilijk kijken, maar vol goede moed was het varkentje uiteindelijk altijd binnen no-time gewassen. Jullie gedrevenheid, enthousiasme en professionaliteit hebben ervoor gezorgd dat we steeds supersnel patiënten hebben kunnen includeren en dat vrijwel alle data gebruikt kon worden. Graag zou ik drie personen specifiek uitlichten: Ankie, bedankt dat je altijd flexibel en enthousiast bent, mede door jou als teamleider is CT altijd een prettige plek om te zijn. Serena, je gaat het zeker weten fantastisch doen! Dank voor al het extra werk dat je voor me hebt gedaan! Jef, bedankt dat je veel slimmer bent dan ik!

Prof. Dr. M.W. de Haan, het heeft even geduurd, maar het lukt me inmiddels al een tijdje om *je* gewoon *Michiel* te noemen. Mijn eerste echte gesprek bij de radiologie was met jou en daarmee is de cirkel met jou als voorzitter van de leescommissie rond, bedankt! De overige leden van de beoordelingscommissie, Prof. Dr. Steven Oldedamink, Prof. Dr. Roger Rennenberg, Dr. Nils Planken en Dr. Doenja Lambregts wil ik eveneens hartelijk danken voor de grondige beoordeling van mijn proefschrift.

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en goed bedachte) cadeautjes, steun, betrokkenheid en heerlijke etentjes, dat er nog maar veel mooie momenten mogen volgen!

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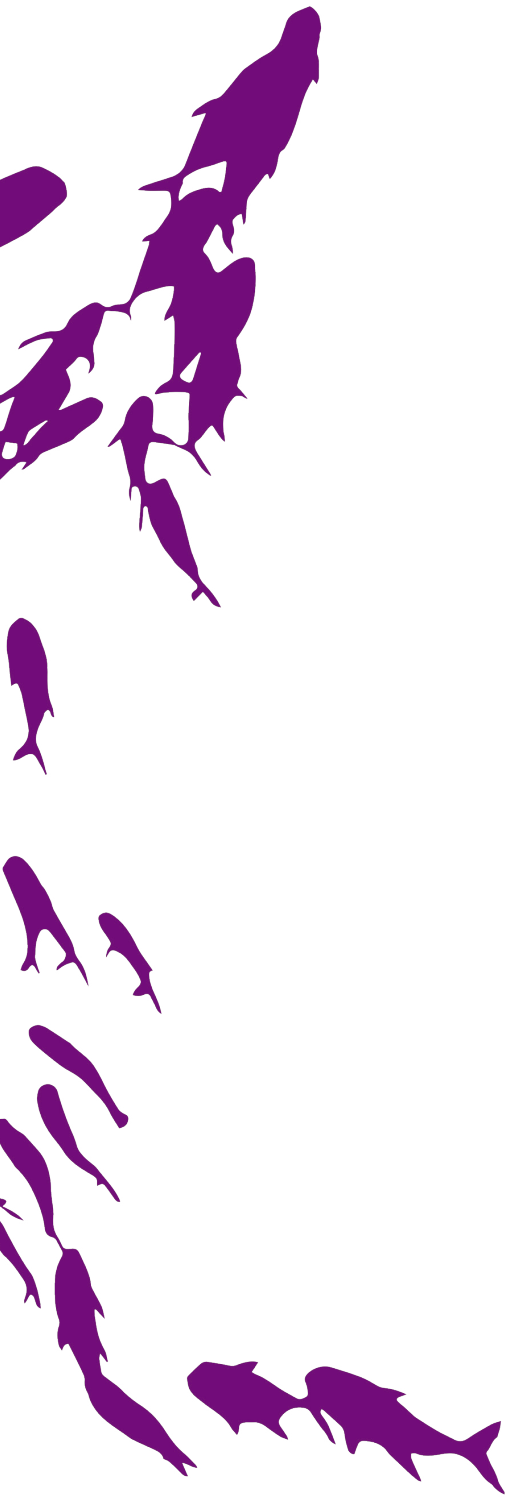

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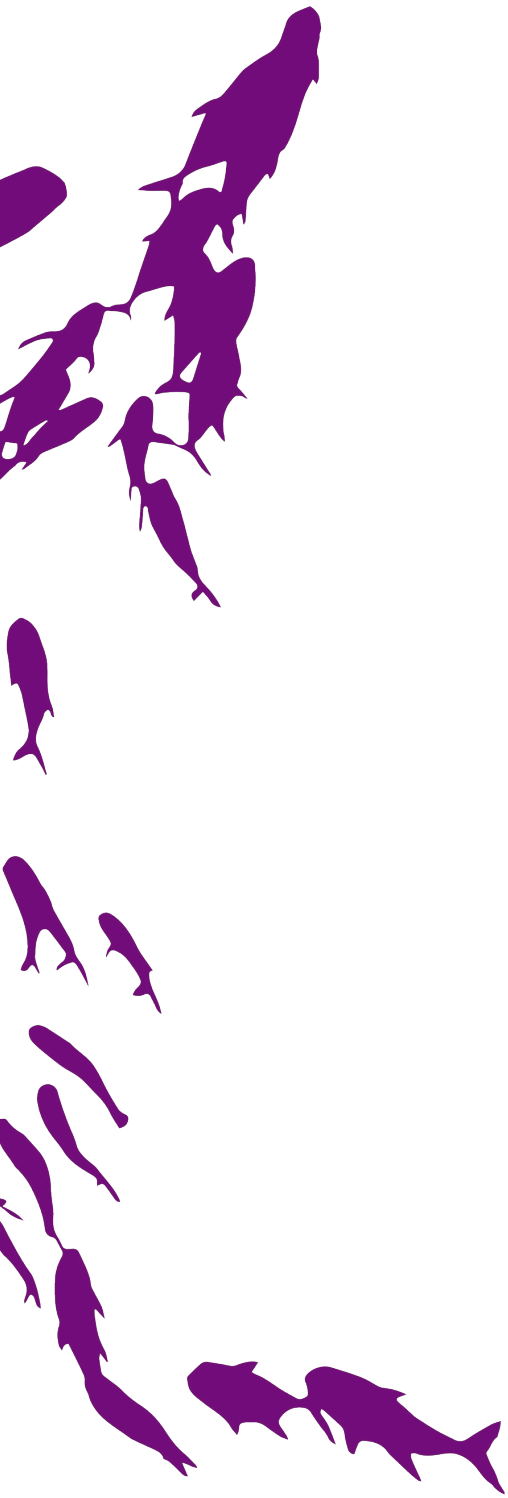
Bibi Martens was born on the 4th of December 1986 in Roosendaal, the Netherlands. In 2005 she graduated from the Strabrecht College in Geldrop, The Netherlands. In the same year, she started at the Faculty of Psychology and Neuroscience in Maastricht with her Bachelor in Psychology, with a 6-month elective internship at James Cook University in Smithfield (Australia). She received her bachelor degree in 2010 and started her medical training at the Faculty of Health, Medicine and Life Sciences at the University of Maastricht in 2008. After obtaining the medical degree in 2014 she started her radiology residency in 2015 at Maastricht University Medical Center (MUMC), under the supervision of dr. A.A. Postma-Jacobi. In 2016 she commenced her PhD project under the supervision of Prof. dr. J.E. Wildberger, dr. C. Mihl and dr. E.C. Nijssen with as a main goal the optimalization of both radiation and contrast media dose in abdominal computed tomography. The results led to present thesis and were presented at several (inter)national congresses. She was awarded for parts of the research with a 'Student Travel Award, for one of the best abstracts during the RSNA annual meeting in Chicago and the 'René Vogels Reisstipendium', which was not used due to the COVID-19 pandemic. She finished her radiology training in January 2021, after which she started as a fellow in cardiovascular imaging at the MUMC. She remains involved in this research topic.



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This thesis

Martens B, Hendriks BMF, Eijsvoogel NG, Wildberger JE, Mihl C. Individually body weight–adapted contrast media application in computed tomography imaging of the liver at 90 kVp. *Invest. Rad. 2019;54(3):177-82.*

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