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OPTIMIZATION OF INTRAVENOUS CONTRAST MEDIA AT COMPUTED TOMOGRAPHY

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Hope and Struggle

Pete Seeger

ABSTRACT

The administration of intravenous contrast media (IV CM) is essential for detecting lesions at most computed tomography (CT) examinations. The overall aim of this thesis is to investigate different aspects of IV CM administration that may affect the quality of the CT examination.

In **Study I** a comparison was made between a low osmolar contrast media (LOCM) iomperol and the iso osmolar contrast media (IOCM) iodixanol, focusing on how they may affect heart rate, heart rate variability, experienced patient heat sensation and image quality at coronary computed angiography (CCTA) in 100 patients. No significant difference in terms of heart rate interfering with the imaging protocol was observed. However, a greater number of arrhythmic heart beats (hb) was observed with the use of LOCM than with IOCM ($P< 0.001$). There was no difference in subjective image quality between the two CM. The experienced heat sensation was stronger when receiving LOCM than when receiving IOCM (visual analogue scale = 36 mm and 18 mm respectively, $P< 0.05$).

In **Study II** the enhancement of liver and aorta was related to different measures of body size and to the use of two different CM (LOCM iomeprol and IOCM iodixanol) in 100 patients undergoing thoraco-abdominal CT. Three parameters had a stronger correlation to the CM enhancement in liver and aorta; Body weight (BW, $r= -0.51$ and -0.64), body surface area (BSA, $r= -0.54$ and -0.65) and lean body mass (LBM, $r= -0.54$ and -0.59), but there was no statistically significant difference between those. The parameters body height (BH), body mass index (BMI) and ideal body weight (IBW) had weaker correlations to CM enhancement of liver and aorta. When adjusting for differences in weight, height, age and sex between the two groups there was a stronger liver enhancement after injection of the IOCM iodixanol than after injection of the LOCM iodixanol (mean difference 6 HU, $p < 0.01$).

Conclusion: The iso osmolar contrast media iodixanol causes less arrhythmic hb and less heat sensation than the low osmolar contrast media iomeprol, but this does not significantly influence the quality at CCTA. The CM enhancement is affected by body size. There is no statistically significant better parameter than BW to adjust for, why this parameter is recommended for dose adjustments. When performing hepatic imaging the IOCM iodixanol might be preferred to the LOCM iomeprol due to a stronger CM enhancement, but confirming studies are required.

LIST OF PUBLICATIONS

I **Heart rate variability and heat sensation at CT coronary angiography: Low-osmolar versus iso-osmolar contrast media.**
Svensson A, Ripsweden J, Rück A, Aspelin P, Cederlund K, Brismar B. T.
Acta Radiol. 2010 Sep;51(7):722-6

II **Hepatic contrast medium enhancement at computed tomography and its correlation with various body size measures.**
Svensson A, Jallo N, Cederlund K, Aspelin P, Nyman U, Björk J, Brismar B. T.
Submitted Acta Radiol.

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LIST OF ABBREVIATIONS

AA	Ascending aorta
AASLD	American Association for Study of Liver Diseases
APASL	The Asian Pacific Association for the study of Liver
BH	Body height
BMI	Body mass index
BSA	Body surface area
BW	Body weight
CCTA	Coronary computed tomography angiography
CIN	Contrast media induced nefropathy
CM	Contrast media
CT	Computed tomography
DSR	Dynamic spatial reconstruction
EBCT	Electron beam computerized tomography
ECG	Electrocardiogram
GFR	Glomerular filtration rate
HOCM	High osmolar contrast media
Hb	heart beat
HU	Hounsfield units
IBW	Ideal body weight
IOCM	Iso osmolar contrast media
IV	Intravenous
LBM	Lean body mass
LEVDP	Left endo ventricular diastolic pressure
LMCA	Left main coronary artery
LOCM	Low osmolar contrast media
MDCT	Multi detector computed tomography
MHE	Maximum hepatic enhancement
P	probability
RCA	Right coronary artery
ROI	Region of interest
VAS	Visual analogue scale

1 INTRODUCTION

1.1 BACKGROUND

A computed tomograph (CT) produces images of the human body by mechanically rotating an x-ray tube and detector array around the patient. When passing through the body the photons in the x-ray beam are taken up differently depending on the density of the tissues. By continuously comparing the amount of photons leaving the X-ray tube with the number of photons detected by the detector when the x-ray tube rotates around the body the theoretical uptake of photons in different parts of the body can be calculated and an image can be constructed. For the development of the CT Godfrey N. Hounsfield and Allan McCormack shared the Nobel prize in medicine and physiology in 1979, Hounsfield for the construction of the CT and McCormack for his work on the reconstruction algorithm. To honour the inventor the attenuation unit describing the photon uptake is called Hounsfield units (HU). The HU is defined by the Hounsfield scale, in which air is -1000 HU (lowest possible) and 0 is defined by the attenuation of water. There is no upper limit of the scale (1, 2, 3).

1.2 INTRAVENOUS CONTRAST MEDIA

1.2.1 The history of intravenous contrast media

In January 1896, shortly after the discovery of x-rays by Conrad Wilhelm Röntgen, the first in vitro angiogram was performed by Haschek and Lindenthal using a solution of bismuth, lead and barium injected into the vessels of an amputated arm (4). During the beginning of 1900s attempts were carried out with different early CM for imaging the renal system. In 1904 Wulff managed to image the urine bladder using retrograde infusion of bismuth subnitrate. The first successfully performed retrograde pyelography was made by Voelecker and Lichtenberg in 1905-06 using colloidal silver (Collargol). However due to injection pressure the use of Collargol could involve serious complications in damaging the renal pelvis causing leakage of silver from the injured kidney. Attempts with other types of solutions, such as thorium nitrate, were carried out by Burns in 1915, but as its forerunner severe complications occurred. In 1923 Osborne and Rowtree showed that sodium iodide used for the treatment of syphilis could also be used as an IV CM for imaging of the urine bladder. In cooperation between the two German chemists, Binz and Räth and the American physicist Swick, the first commercial hydrophilic IV CM, Uro-Selectan (Schering-Kahlbaum), was introduced in 1929 (5, 6).

1.2.2 Contrast media induced adverse reactions

The only desirable effect wanted from IV CM is the attenuation of x-ray photons, all other effects are to be consider as secondary or toxic effects.
CM can be divided into four different groups; 1) ionic monomers 2) ionic dimers 3) non-ionic monomers 4) non-ionic dimers (Figure 1).

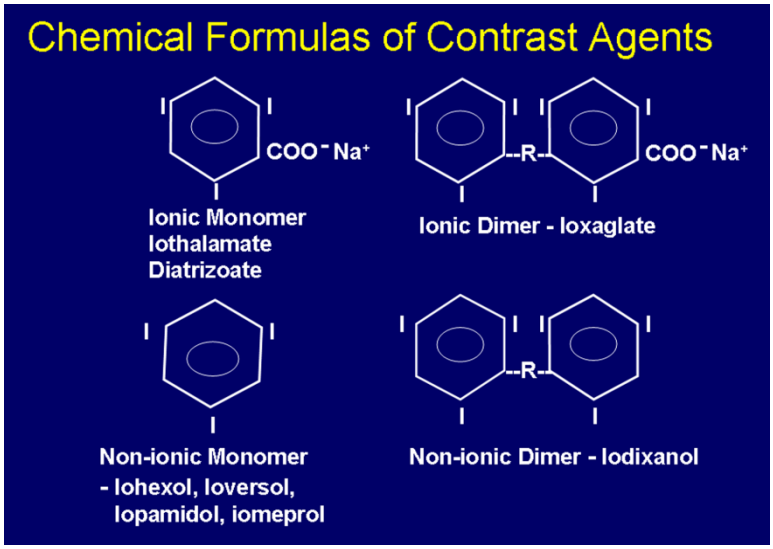


Figure 1. Chemical formulas of contrast agents (7).

CM toxicity refers to the sum of 4 influencing factors:

1) *Osmotoxicity*. Osmotic effects caused by a CM affect the water transport across cell membranes. The osmotic effect (Figure 2) of a CM is related to the ratio of iodine atoms per molecule. A higher ratio, ie more iodine atoms per molecule, causes a lower osmotic pressure and thereby a lower osmotoxicity. This is because a less number of molecules are needed to obtain the same iodine concentration. Previous angiographic studies have shown that HOCM cause more cardio and pulmonary events, such as increased heart rate and/or breathing rate, and a greater decrease in arterial pressure than LOCM do. The osmotoxicity of HOCM may also lead to an aggregation of red blood cells. This can act as emboli and may block the pulmonary blood circulation in patients with pulmonary hypertension. Osmotoxicity may also induce neurotoxic reactions such as spasm and unconsciousness. Moreover, the experienced heat sensation and pain in association with the CM injection has been shown to be substantially worse with HOCM.

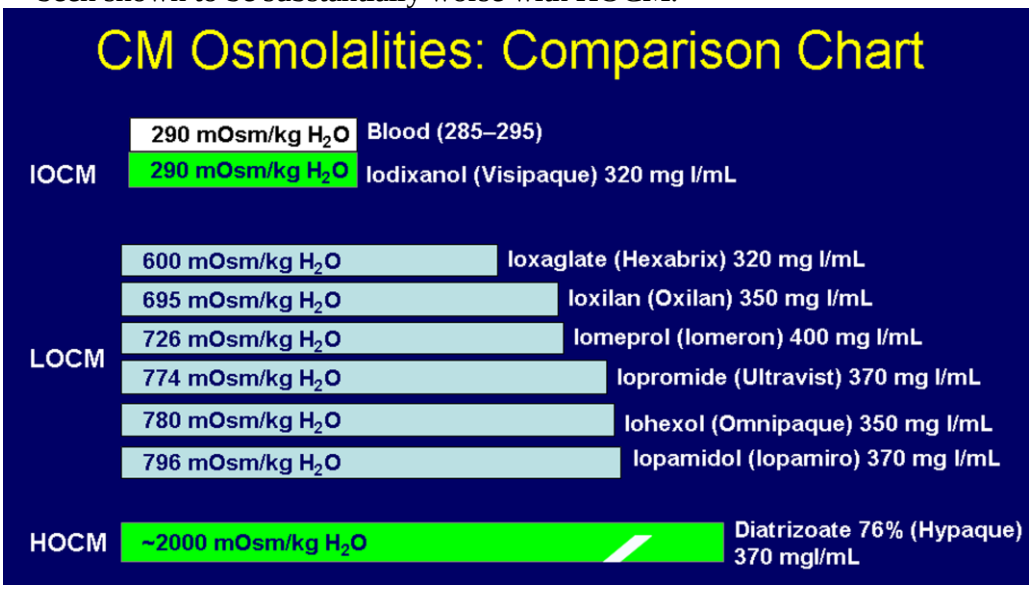


Figure 2. CM osmolalities, comparison chart (8, 9).

2) *Ionic toxicity* refers to the electrolyte content of the CM. Changes in electrolyte concentrations may lead to a reduction in cardiac contractibility and/or induce arrhythmia, which in worse scenarios may lead to ventricular fibrillation. Different types of chelating agents of CM could affect the concentration of free calcium ions and thereby influence cardiac hemodynamics.

3) *Viscosity* describes the ability of a fluid to resist flow. The viscosity of a CM is determined by the concentration of iodine (mg/ml), molecular weight of the solute, and the molecular shape. The chemical tolerance of the CM is also affected by the viscosity. IOCM have a greater viscosity than that of the same concentration of LOCM, resulting in the need of a higher injection pressure. This can potentially affect the possibility to obtain a high injection rate. Since viscosity also is dependent on temperature, heating of a CM can substantially decrease its viscosity and thereby facilitate higher flow rates (Table 1).

Table 1. CM dynamic viscosity (centi poise, cP) (10, 11)

Contrast media	20°C **cP**	37°**C cP**
Iohexol (Omnipaque® 300mgI/ml)	11.8	6.3
Iodixanol (Visipaque®320mgI/ml)	26.6	11.8
Iomeprol (Iomeron® 400mgI/ml)	27.5	12.6

4) *Chemotoxicity* is the sum of -osmo, -ionic toxicity and viscosity which may lead to a disturbance of normal cell functions, interact with plasma proteins and cause pseudo allergic reactions through a release of vasoactive substances. The chemotoxicity is affected by the presence or absence of hydroxyl groups wich are added to improve hydrophilic capability of the CM.

The pH value of the IV CM is also of importance, where a low pH may lead to vasodilation and hypotension. (12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24).

CM induced nephropathy (CIN) is a well-known complication to the use of IV CM. The complication predominantly affects patients with reduced renal function. The generally accepted threshold for increased CIN risk is defined as a glomerular filtration rate (GFR) of <45ml/min/1.73 m². Patient related risk factors for CIN are; elderly patients, chronic kidney disease, diabetic, severe cardiac failure and dehydration. Previous studies have shown a greater frequency of CIN when using HOCM in comparison to LOCM (25).

1.2.3 The development of new intravenous contrast media

Pioneer work during the 60s performed by Torsten Almén lead to the development of the first non-ionic monomer LOCM metrizamid (Amipaque, Nygaard & Co, Norway) which was introduced in the 70s. In comparison to previously used ionic HOCM Metrizamid demonstrated a significant reduction of all adverse reactions and almost eliminated the pain associated with angiography. However, the sterilization process (autoclaving) made the CM molecule unstable when in solution so the CM had to be distributed as a powder to be mixed with water prior to the x-ray examination. To avoid this inconvenience the LOCM monomer iohexol (Omnipaque®, GE healthcare, Chalfont St Giles, UK) was marketed in the 1980s. The first non-ionic iso-osmolar CM (IOCM) iodixanol (Visipaque, GE Healthcare, Chalfont St. Giles, United Kingdom) was introduced during the 1990s. Iodixanol has the same osmolality as blood, plasma, and cerebrospinal fluid (9).

1.3 COMPUTED TOMOGRAPHY (CT)

1.3.1 The development of spiral and multidetector computed tomography (MDCT) technology

The development of spiral or helical CT technology during the end of 1980s and beginning of 1990s made huge impact on radiology. It was made possible by the introduction of the 'slip ring' technology in 1987 (Somatom Plus, Siemens Medical Systems, Germany and TCT 900S Thoshiba Medical Systems, Japan) that allowed the x-ray tube and detector to rotate without any power supplying cable interfering with the rotation. The spiral, or also so-called helical technique, was for the first time presented in 1989 and it replaced the old 'step and shoot' technique. At spiral scanning there is a continuous X-ray tube and detector rotation during a continuous table movement. This lead to a significantly reduced scan time (26) and improved the examination quality by reducing motion artefacts. For the patients this also meant higher comfort, because breath hold duration could be reduced (27).

In the end of the 1990s the first multi detector computed tomography (MDCT) system was presented. The detector in these systems consists of several rows of detector elements. These reduce the scan time because the coverage per rotation is much higher than that of single detector systems. During the last decade CT vendors have presented MDCT systems with an increasing number of detector rows; from 4 to 16, 32, 64, 128, 256 to 320 rows (28, 29, 30, 31).

During the last few years dual energy MDCT systems have been introduced. With these systems the same anatomical section is scanned (almost) simultaneously with different kV-settings (e.g. 80 and 140 kV) which potentially enables better tissue characterisation. Example of applications for dual energy is urine stone characterization, gout diagnosis, bone subtraction, virtual non-contrast studies, dual energy cardiac perfusion, metal artifact reduction etc. The technical solution behind simultaneously dual energy scanning is somewhat different between MDCT manufacturers. The Siemens Definition Flash system (Siemens Medical Systems, Erlangen, Germany) uses two separate x-ray tubes and detectors while the GE Discovery 750 HD (GE healthcare, Milwaukee, USA) uses fast kV-switching during the gantry rotation (32).

1.3.2 Optimization of contrast media enhancement at CT

Although the CT image was revolutionary for visualizing the organs it could be further improved by using IV CM. The CM used in clinical practise are based on iodine. Iodine has a very high attenuation and it can therefore be used to visualize the vascularisation of the tissue after injection into the vascular system. The enhancement from the CM is defined as an increase in Hounsfield enhancement (HU-enhancement).

The administration of CM during CT is today regarded as crucial for detecting parenchymal lesions. There are several physiological factors that affect the CM enhancement where body size (body weight, BW and body height, BH) and cardiac output are the most important. Other factors that may contribute to the CM enhancement is age, gender, hepatic chirrosis, renal function, and portal hypertension. Also technical factors have great influence on CM enhancement, e.g. injection rate (ml/s) and CM volume (ml). To achieve the highest accuracy when detecting pathology at CT all these factors must be optimised (33, 34, 35, 36, 37, 38, 39, 40).

For all used IV substances there is a potential risk of side effects. Studies performed during invasive coronary angiography (ICA) have shown a larger proportion of hemodynamic changes using high osmolar (HOCM) CM in comparison to low osmolar (LOCM) CM (41, 42, 43, 44) (Figure 3). There have also been reports describing higher incidence of hemodynamic changes using LOCM in comparison with iso osmolar (IOCM) (45, 46). When performing coronary computed tomography angiography (CCTA) a stable and low heart rate is of great importance to ensure optimal image quality (Figure 4). In order to reduce the heart rate ß-blockers are often used at CCTA imaging, even when the patient has no such prescription previously (47). If the CM affects the hemodynamics it may also affect the heart rate, and thereby affect the image quality. If the choice of CM affects the hemodynamic changes it may also have an impact on patient discomfort. This has previously been observed in angiographic studies where a greater frequency of discomfort e.g. pain and heat sensation has been observed when using HOCM in comparison to LOCM (48)and when using LOCM in comparison to IOCM (49, 50).

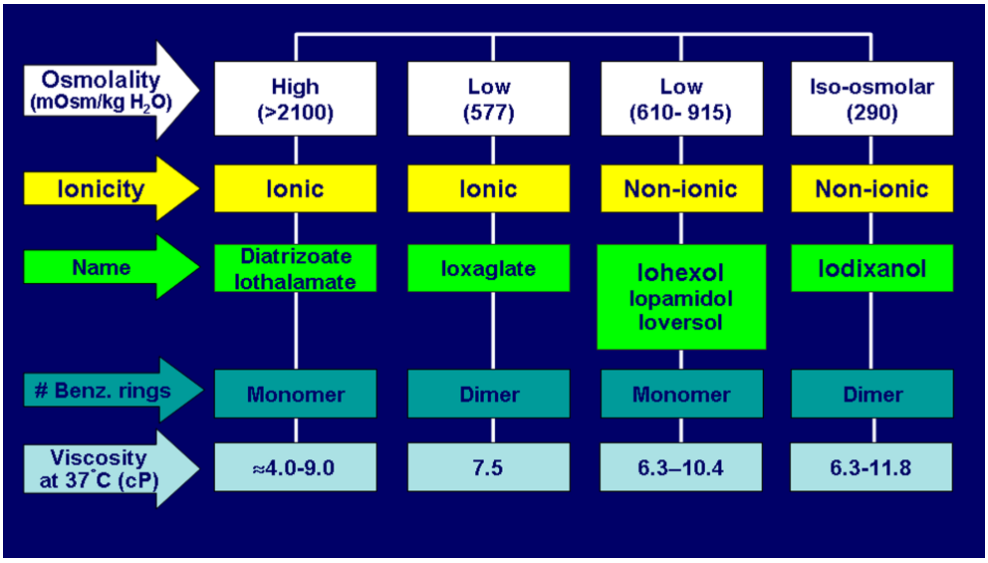


Figure 3. Intravenous contrast media classification (7, 51).

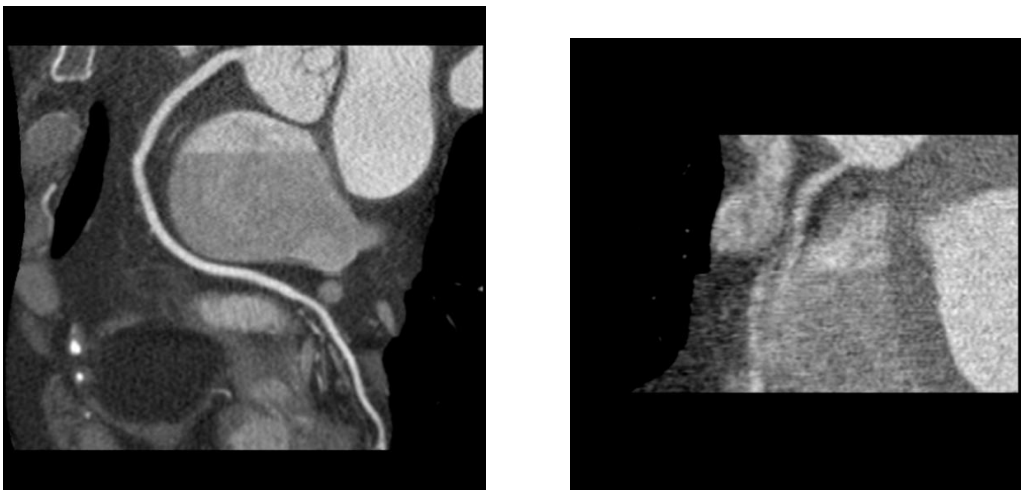
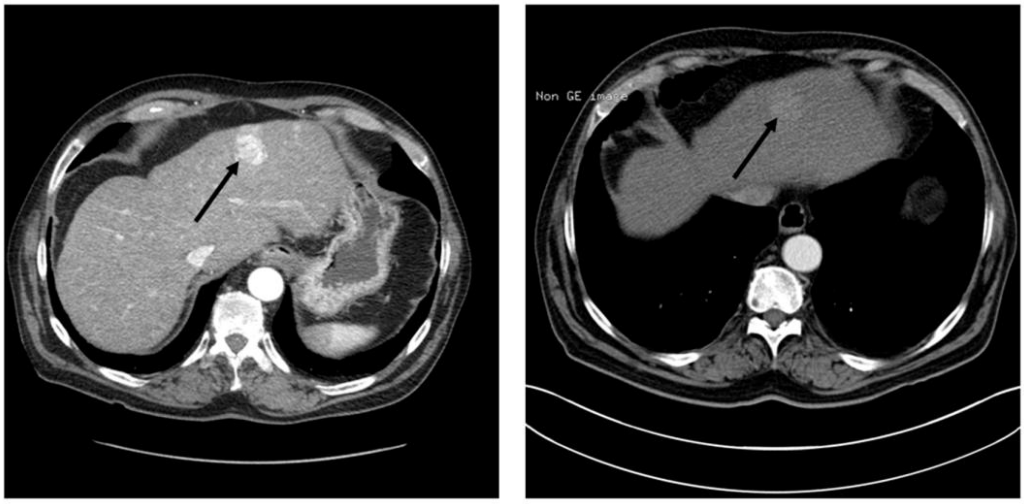


Figure 4. (a) Right coronary artery (RCA) (b) hampered due to motion artifacts.

Lesions in the liver may be hypo or hyper vascular. In order to detect subtle differences in vascularisation between normal liver and pathologic lesions it is of great importance that the administration of the CM is optimal (52, 53, 54, 55) (Figure 5). Traditionally the same amount of CM has been given to all patients. However, the blood volume, into which the CM is diluted is closely related to the body size. The relationship is not linear, but because of different body composition the BV will differ between obese and muscular individuals due to low perfused fat tissue which may lead to CM overdosing in obese individuals (56, 57, 58).

Therefore instead of the fixed CM dosage a more individualized CM dosage has been suggested. The idea is to have a more uniform CM enhancement independent from body size (59). By applying an individualized CM dosage the risk of side effects associated with CM can be reduced. This is especially important in elderly patients with reduced kidney function, ie a reduced glomerular filtration rate (GFR) (60). Elderly patients often have a lower BW and therefore have a greater risk of CM overdose than younger patients. Several different formulas have been proposed for calculating individual CM dosage based on body size (61, 62, 63, 64, 65, 66, 67, 68, 69, 70,71), but there is no general agreement on which formula that results in the most optimal individual dosage.



a **b**

Figure 5. Same patient scanned at different hospitals (hyper vascular liver lesion). Optimal CM timing and dosage (a), insufficient CM administration (b).

1.4 CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY (CCTA)

1.4.1 The development of ECG gated cardiac scanning

In 1974 a research group in Japan succeeded in performing the first ECG gated cardiac examination using electron beam computerized tomography (EBCT). Instead of using a conventional X-ray tube the electrons were generated by an accelerator and then focused on targeted rings generating X-ray radiation. The technique was improved during the late 70s and the first commercial equipment was introduced in 1980 (General Electric Imatron C 150). The temporal resolution, i.e. the acquisition time, was at that time in comparison with conventional CT scanners very fast. The main application for EBCT was to quantify calcifications in coronary arteries, so-called calcium scoring (Ca-scoring). However, the EBCT technique was expensive and had a low resolution, why the technique did not reach any general use.

The dynamic spatial reconstructor system (DSR) or the so called ¨The Mayo monster¨ was presented in the early 1980s. It was able to reconstruct 240 simultaneous 1mm slices collected from 14 separate x-ray tubes. The DSR system was designed for visualization of heart and lungs, but because of its costs and size, 14 ton, DSR never became a commercial product.

The modern era of cardiac imaging started with the introduction of MDCT scanners in the late 1990s, when a shorter acquisition time and a better temporal resolution could be achieved. Since then the quality of cardiac imaging has continuously improved (72, 73, 74).

1.4.2 CCTA 64 row MDCT technique

In order to perform good cardiac imaging the contraction phase of the heart must be taken into account. This is achieved by using ECG gating / triggering. By recording the ECG signal the CT scanner can reconstruct images at the correct time intervals. The so-called R peak of the ECG recording is used to identify the time-point of maximum cardiac contraction. At the time of our study there were two possible scanning techniques available;

Retrospective (spiral technique)

At retrospective technique data is sampled during the whole R to R interval with the use of low pitch scanning (a slow table speed in relation to X-ray tube rotation) (Figure 6). Due to this oversampling of data, images from all time points of the R to R interval can be reconstructed, which is important if changes in heart rate occurs during scanning. However, the disadvantage with this technique is the radiation dose (75, 76). Normally only XX% of the sampled data is used to obtain the diagnostic images. Therefore the ECG-dose modulation was introduced to reduce the high radiation dose associated with earlier retrospective gated technique.

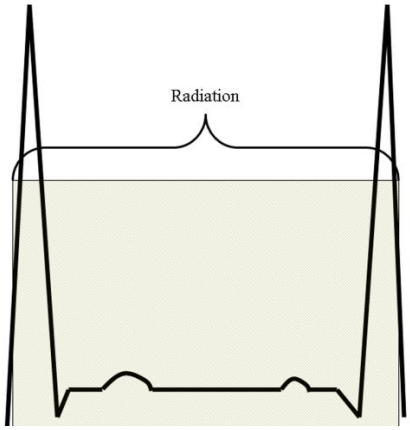


Figure 6. Retrospective gating. Spiral scanning. Through the whole R-R interval makes it possible to reconstruct data from every time point of the heart cycle.

At ECG dose modulation the diastolic portion of the R to R interval is scanned using a high radiation dose, allowing optimal image quality, and during the other parts of the cardiac cycle a lower radiation dose is used (77) (Figure 7). Depending on patient heart rate there are different options for the gated retrospective technique. The so called segmental half scan technique uses data from one heart cycle to create images. When the heart rate exceed the limits for the segmental half scan technique data arecollected from more than one heart cycle. The disadvantage with this technique is image quality is very dependent on a stable heart rhythm (78).

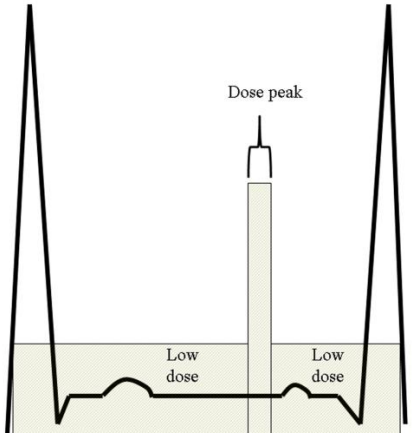


Figure 7. ECG-dose modulation. Highest mA-peak at the diastolic part of the R to R interval.

Prospective-gated technique (axial or ¨step and shoot¨ technique)

In the prospective gated technique a portion of the R to R interval e.g. diastole is scanned (Figure 8). The advantage with this technique in comparison to the retrospective gated technique is the lower radiation dose. When using the prospective-gated technique a 77-87 % radiation dose reduction with equal to significantly improved image quality has been reported (79).

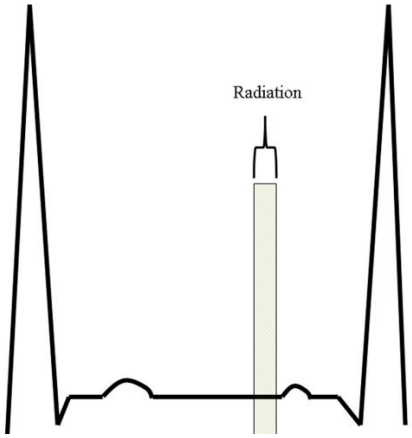


Figure 8. Prospective gating, axial or ¨step and shot¨ technique. Scanning over the pre defined portion of the R-R interval (diastole).

1.4.3 CCTA contrast media injection protocol

Dual flow, or so called tri-phasic CM injection protocol, has shown to be superior in comparison with mono- or bi-phasic injection protocols in terms of visualization of the right side of the heart and the prevention of streak artifacts origin from vena cava superior. The tri-phasic injection protocol consists of three injection phases. The first

phase is the pure CM bolus injection meant for enhancing the left side of the heart including coronary vessels. The second phase is the mixed phase, saline and CM, in which the right side of the heart is enhanced. The third phase consists of a saline flush by which all CM is pushed forward, emptying vena cava superior from dense CM, preventing streak artifacts (80, 81, 82, 83).

1.4.4 Patient preparation and pitfalls in 64-row MDCT CCTA

Patient specific parameters that affect image quality at CCTA are; heart rate and variability in heart rate, patient cooperation, patient size and calcified plaques. For an optimal CCTA study an ideal patient should therefore be non-overweight, able to follow the instructions, have a low and stable heart rate and have an absence of large coronary calcified plaques (84).

The injection of CM intravenously is most often made through an inserted peripheral vein catheter. Studies have shown a better HU-enhancement when a proximal (antecubital vein) position is used compared to a distal position (85). It has been shown that heart rate in average decreases about 4 heart beats during patient apnoea (86). To determine the breath hold capability and heart rate during apnoea breathing exercises are therefore made in association to the CT examination so that the most optimal scan protocol can be selected. The patient preparation and cooperation is therefore of great importance for the outcome of the CCTA. The presence of trained and experienced radiographers in this process may therefore have an impact on the outcome of the scanning (87).

1.5 VISUAL ANALUOGE SCALE (VAS)

The use of the visual analogue scale (VAS) as a tool for measuring health outcome has been well established since the early 1970s. The phrase *feeling thermometer* was first expressed in the beginning of the 1980s and since then a number of different approaches for VAS have been created (length of line, scale marks, vertical or horizontal placement of the line, anchored endpoint of the line) (88, 89).

1.6 DIFFERENT BODY SIZE MEASURES

1.6.1 The origin of body mass index (BMI), ideal body weight (IBW), lean body mass (LBM) and body surface area (BSA)

The classification of human body size has a long history, initially aiming on describing under- and overweight and also to define desirable or ideal weight. During history obesity has been considered as a sign of good health. However this opinion started to change during late 18^{th} and 19^{th} century because of observed complications associated to obesity. In 1913 one of the first height-weight tables were published based on actual data derived from measurements (with shoes and cloths on) of life insurance policyholders (90, 91). There are several models for measuring body size.

The probably most well-known model for measuring body size, besides body weight, is body mass index (BMI, Table 1). The constructor of the equation was the Belgian mathematician and astronomer Adolphe Quetele (1796-1874). The equation became commonly used by American insurance companies during the period after the Second

World War (1945) (92). Findings recorded by insurance statistical experts showed a clear relationship between obesity and increased mortality. Using that index, overweight is defined as a BMI of 25 to 30 kg/m^2 and obesity as a BMI above 30 kg/m^2 (93).

The equation for ideal body weight (IBW) according to Devine (Table 2) was originally designed for the estimation of gentamicin clearance in obese patients. Due to the adverse effects associated with the accumulation of the antibiotic drug gentamicin, overdosing obese patients and/or patients with renal dysfunction could in worse cases lead to nephrotoxicity and ototoxicity (94). IBW has been shown to be superior to several other body measurements when calculating drug dosage in obese patients (95)

The parameter fat free mass, or more commonly lean body mass (LBM), refers to the total weight of muscles, organs and bones, excluding fatty tissue (96, 97). The available technical methods for measuring LBM include whole-body densitometry by underwater weighing, bioelectrical impedance analysis (BIA), dual-energy x-ray absorptiometry (DEXA) and skinfold thickness (98). A simplified LBM can be calculated by using the formula developed by Hume (99) and by James (100). Those are both easily accessible but in comparison to technical measurement not as accurate (101).

The equation for body surface area (BSA) was published by Du Bois et al in 1916 (102). The equation is still commonly used in clinical practice, particularly for the calculation of chemotherapy doses and for normalizing physiologic parameters such as cardiac output, left ventricular mass and GFR (103, 104, 105). The equation derives from a very limited number of subjects, only nine, but has been widely used over the years. A simplified equation for BSA (Table 1) was published in 1987 by Mosteller (106). The Mosteller formula has been shown to be more accurate than the DuBois formula in the estimation of obese patients. The equation is also convenient to handle in daily clinical practice, easily calculated using a pocket calculator (107).

Table 2. Body size equations.

Equation	
Body mass index	Men and Women: Weight (kg)/(Height $(m)^2$)
Lean body weight, James (kg)	Men = 1.10 × Weight (kg) - 128 ×$Weight^2$/$Height\ (cm)^2$ Women = 1.07 × Weight (kg) - 148 × $Weight^2$/$Height\ (cm)^2$
Lean body weight, Hume (kg)	Men: 0.3281 × Weight (kg) + 0.33929 × Height (cm) – 29.5336 Women: 0.29569 × Weight (kg) + 0.41813 × Height (cm) – 43.2933
Ideal body weight Devine (kg)	Men: 50 + 2.3 × (Height (cm)/ 2.54 – 60) Women: 45.5 + 2.3 × (Height (cm)/2.54 – 60)
Body surface area Dubois (m^2)	Men and Women: 0.007184 × $Height\ (cm)^{0.725}$ × $Weight\ (kg)^{0.425}$
Body surface area Mosteller (m^2)	Men and Women: [Height (cm) × Weight (kg)/3600]$^{0.5}$

1.7 CT LIVER IMAGING

1.7.1 Factors influencing CM enhancement in liver

By using CM it is possible to rule out thromboses in the liver vessels and to better depict tumours (108, 109). It has been shown that by increasing the amount of injected iodine (gI) within the same patient an improved CM enhancement of the liver parenchyma can be achieved (110). For each patient the maximum hepatic enhancement (MHE) is desired, but the toxic side-effects must also be taken into account. In order to achieve a satisfactory diagnostic safety at least 50 HU enhancement is desirable (111). Another factor affecting the CM enhancement, beside the total injected amount of iodine, is the injection rate (ml/s). A faster injection rate results in a higher CM enhancement during the late arterial or portal venous inflow phase than that of a slower injection rate (112).

Cardiac output is one of the physiological factors that may affect the CM enhancement of the liver. Bae et al. showed that the time to MHE increased with 70s when cardiac output was reduced with 55% (113). To compensate for inter and intra patient variation in cardiac output so called bolus tracking is used in daily clinical practice. In clinical practise a HU threshold value is defined and a region of interest (ROI) is placed in a vessel, most often in aorta. Monitoring scans are then applied and the acquisition starts immediately, or after a defined scan delay, when the HU threshold value is reached (114).

Improvements in the area of MDCT technology has made it possible to perform multi phase CM imaging, enabling the detection and characterisation of different focal liver lesions. For example, when diagnosing hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma there are consensus guidelines from The American Association for Study of Liver Diseases (AASLD) and the The Asian Pacific Association for the study of Liver (APASL) recommending a pre-contrast study, hepatic arterial phase, portal-venous phase and a delayed phase (¨wash out¨ phase) (115). However, the CM timing is crucial for the detection (116). When applying a two-phase liver CM protocol the typical delay in scanning, after reaching the threshold value in aorta, would be 40 seconds for detection of hypervascular lesions and 70 seconds for the detection of hypovascular lesions (117, 118).

2 AIMS OF THE THESIS

The overall purpose of the research described in this thesis was to investigate how CM osmolarity and body composition affects image quality and patient comfort.

Specific aims:

Paper no: 1 To evaluate whether an iso-osmolar contrast medium (IOCM, iodixanol) and a low osmolar contrast medium (LOCM, iomeprol) affect heart rate, heart rate variability, image quality and experienced heat sensation differently.

Paper no: 2 To evaluate if any of the measures body height (BH), body mass index (BMI), lean body mass (LBM), ideal body weight (IBW) and body surface area (BSA) correlated better than body weight (BW) with hepatic enhancement, and to compare the enhancement when using iodixanol and iomeprol.

3 MATERIAL AND METHODS

3.1 PATIENTS

Study I: Between November 2005 and June 2007 100 patients scheduled for CCTA at the Karolinska university hospital in Huddinge were enrolled in the study. In total 63 males and 37 females, aged 51-85 years with a mean age of 63 years were enrolled (Table 3). All examinations were performed by two radiographers with >10 years and >20 years of CT experience respectively, but without previous CCTA experience.

Study II: Between November 2008 and February 2012 100 patients referred for a IV CM MDCT examination at the Karolinska university hospital in Huddinge were enrolled in the study. Of the patients 58 were males and 42 were females, aged 35-89 years with a mean age of 64 years (Table 4).

In both studies patient body weight (kg) and body height (cm) were obtained and recorded. Exclusion criteria included earlier documented adverse allergic reactions to IV CM or an estimated GFR below 50 ml/min according to Cockcroft-Gault formula (119). In study I atrial fibrillation and earlier by-pass surgery also constituted exclusion criteria. Both studies were conducted after approval from the local ethic committee at Karolinska Institutet and all patients gave their written consent.

Table 3. Patient characteristics (Study I) given as median values with 2.5 – 97.5 percentiles.

Parameters	All (n=100)	Women (n=37)	Men (n=63)
Age (years)	62 (51-78)	62 (51-76)	63 (52-78)
Body weight (kg)	78 (57-105)	69 (54-98)	82 (64-108)
Height (cm)	172 (157-188)	164 (154-172)	175 (161-188)
Body mass index (kg/m^2)	26 (21-35)	26 (21-36)	27 (21-34)
Lean body mass (kg)	54 (46-65)	53 (45-64)	55 (46-65)
Ideal body weight (kg)	63 (52-77)	61 (51-68)	66 (53-78)
Body surface area Mosteller (m^2)	1.93 (1.61-2.31)	1.76 (1.55-2.09)	2.0 (1.71-2.32)

Table 4. Patient characteristics (Study II) given as median values with 2.5 – 97.5 percentiles.

Parameters	All (n=100)	Women (n=42)	Men (n=58)
Age (years)	65 (35-84)	65 (36-78)	66 (35-86)
Body weight (kg)	72 (50-112)	65 (50-107)	80 (53-112)
Height (cm)	170 (155-190)	166 (153-175)	176 (162-192)
Body mass index (kg/m^2)	24 (18-35)	24 (18-36)	25 (18-34)
Lean body mass (kg)	53 (41-77)	46 (40-55)	61 (45-79)
Ideal body weight (kg)	65 (48-84)	57 (46-66)	71 (58-86)
Body surface area Mosteller (m^2)	1.83 (1.52-2.38)	1.72 (1.52-2.26)	1.96 (1.56-2.45)

3.2 METHOD

In both studies all examinations were performed using a 64 row detector GE Light Speed VCT (GE Healthcare, Milwaukee, Wisc., USA). Each detector row had a coverage of 0.625 mm, resulting in a 40 mm coverage per rotation. A dual head auto injector (Medrad, Stellant Dual Head Injector,Pittsburgh, Pa., USA) was used for all IV CM injections. Two IV CM were used in both studies, one IOCM (iodixanol 320 mg I/ml (Visipaque ® -320, GE Healthcare, Chalfont St Giles, UK)) and one LOCM (iomeprol 400 mgI/ml (Iomeron ® -400, Bracco Imaging SpA, Milan, Italy).

3.3 STUDY I

3.3.1 Patient preparation

Patients were informed in writing to avoid caffeine (120) and nicotine for 4 hours prior to the CT examination in order to avoid the effect on heart rate that these substances otherwise may had caused. At the CT suite one 18-gauge peripheral venous catheter was inserted in the right or left antecubital vein and connected to the syringes via a tubing catheter to the CM injector. ECG leads were placed at the middle of both clavicle bones and in the left lateral thoracic position. Breathing exercise maneuver took place with the patient positioned on the CT examination table. The patients were informed to take a deep breath and to stop breathing. The breathing exercise was executed for controlling the breath hold capacity and for observing and recording the heart rate during apnea. The heart rate for each heart beat was automatically calculated by the CT system by measuring the time elapse between two R-R intervals (Figure 9).

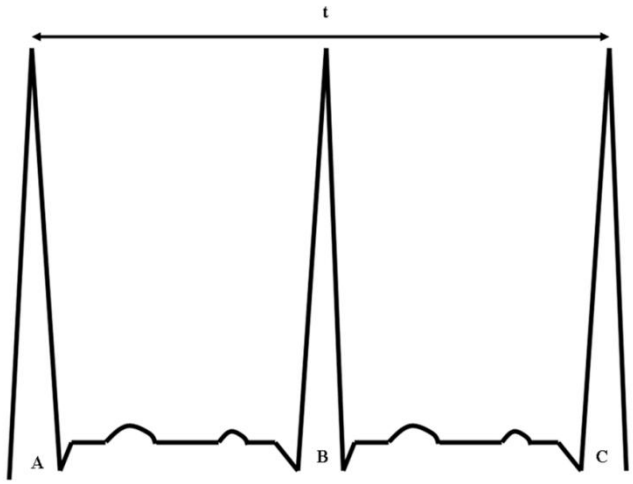


Figure 9. The heart rate at peak B was calculated as 2/t, where t is the time between peak A and C (in minutes).

3.3.2 Scanning parameters and technique

All CT examinations were performed using the retrospective segmental ECG gated scanning technique, which means that every single reconstructed image originates from one single heart cycle. The tube current was set to 120 kVp for all examinations and ECG modulated mA was used with the highest mA peak (650 mA) at 70-80% of

the R-R interval and the lowest was set to 250 mA when outside the predefined diastolic interval (Figure 10). For each patient the scanning protocol was chosen based on the recorded heart rate during the apnea exercise prior to scanning. There were five different protocols, based on five different ranges in heart rate, each with a pitch optimized for that heart rate (Table 5). The scan range was planned on anterior-posterior and lateral overviews with the start position at the level of the tracheal bifurcation covering the whole heart during patient apnea. The patients were asked approximately 10 s before scan start to take a deep breath and then to stop breathing. All sampled data was retrospectively reconstructed into datasets visualizing the heart in 10% phases (0-90%) during the entire heart cycle. The obtained images in the data sets had a 0.625 mm slice collimation and a 0.625 mm increment.

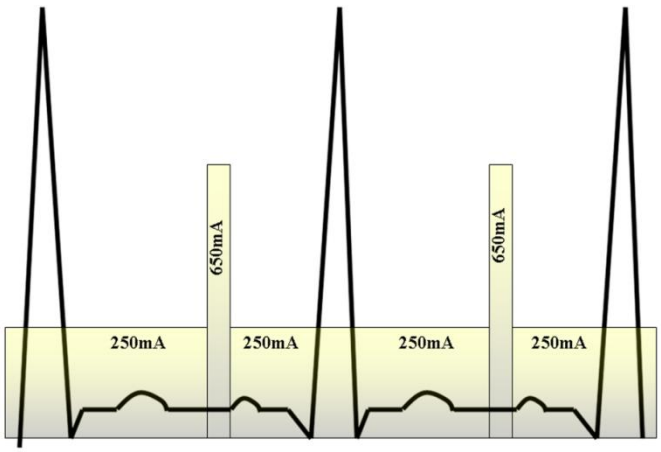


Figure 10. ECG dose modulated retrospective gating with the highest mA peak applied at 70-80 % of the R-R interval.

Table 5. The selection of pitch to use was based on heart rate recorded before scanning.

Heart rate	Pitch	Iodixanol (no. of patients)	Iomeprol (no. of patients)
30-40	0.16	2	0
41-49	0.18	6	9
50-57	0.20	12	12
58-65	0.22	16	11
66-74	0.24	14	18

3.3.3 Intravenous contrast media technique

Using sealed envelopes the patients were randomized prior to the CCTA examination to receive pre-heated CM either iodxianol 320 mg I/ml (Visipaque ®-320, GE Healthcare, Chalfont St. Giles, United Kingdom) or iomeprol 400 mg I/ml, (Iomeron®-400, Bracco Imaging SpA, Milan, Italy). The optimal scanning window was defined by using a test bolus injection protocol containing 20 ml of CM and 20 ml

of physiological saline (NaCl) with the injection rate of 5ml/s. Time to peak enhancement of ascending aorta was calculated by using a 20 mm circular region of interest (ROI). In order to compensate for the larger amount of CM used in the CCTA examination, compared to the bolus, a 7s delay was added to the calculated time to peak. During the CCTA examination the same CM volume was injected at 5ml/s for both iodixanol and iomeprol by applying a 3-phase injection protocol. During the first phase a 50 ml CM bolus was used, then during the second phase a mixture of 20 ml CM and 30 ml of physiological NaCl was injected, followed by a 50 ml physiological NaCl flush during the third phase.

3.3.4 Visual analog scale analysis

After completing the scanning procedure the patients were asked to fill in a questionnaire using the visual analog scale (VAS) regarding their experience of heat sensation associated with the CM injection. The scale ranged from "none" to "worst possible", where no experience of heat was 0 mm and the worst possible heat sensation was 100 mm (49) (Figure 11). The sensation experienced was marked using a pencil. The scale was then measured using a dedicated ruler.

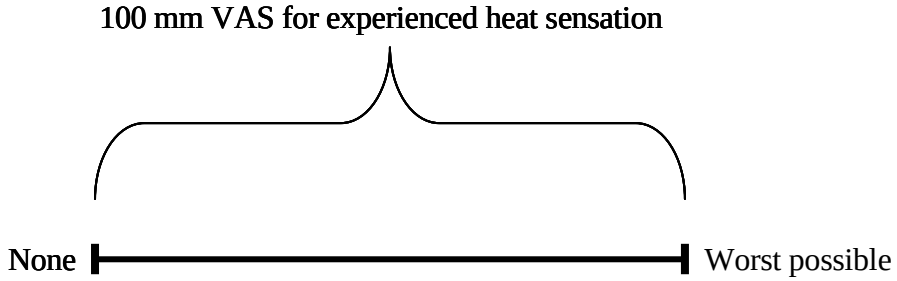


Figure 11. Visual analogue scale (VAS) for experienced heat sensation.

3.3.5 Heart rate and variability analysis

During scanning the heart rate was automatically recorded using dedicated CT ECG leads. The CT system stored the heart rate obtained for each hb with the respective image and it was automatically written out on the displayed images at evaluation. All reconstructed images from the CT scanner were sent to the PACS and to the dedicated work station for analysis (ADW 4.3, GE Healthcare, Milwaukee, Wisc., USA).

To obtain the individual heart rate and its variation during scanning, the following method was used. The table position and displayed heart rate at the position 20 mm superior to the origin of the left anterior descending artery (LAD) were noted. The images were then reviewed and the positions when the heart rate changed were recorded until to the most inferior image of the heart. Each position where a change in heart rate occurred indicated a new hb (Figure 12).

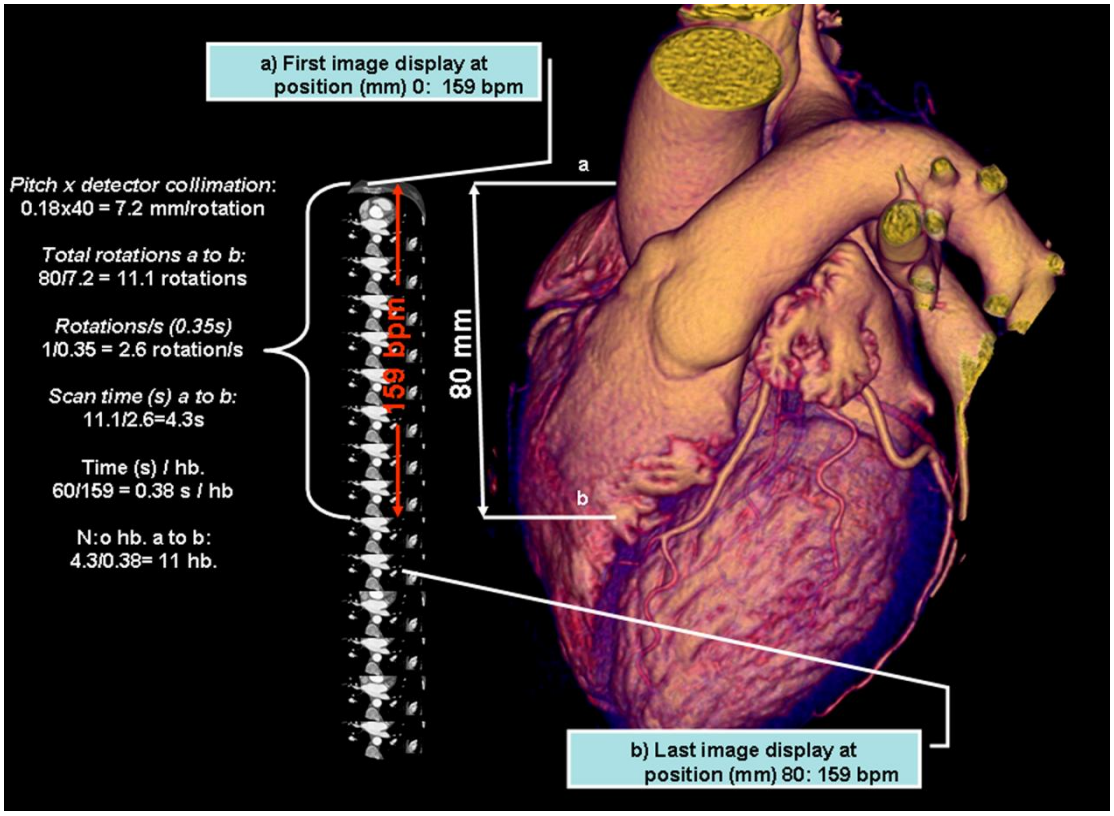


Figure 12. Example on how the number of heart beats was calculated between two positions.

The total number of hb faster than 80 and faster than100 hb/min was counted for each CM. The deviation in individual heart rate from the permitted heart rate range defined in the scan protocol (Table 5) was noted for each hb, and the mean absolute deviation was calculated for each CM.

3.3.6 Image quality assessment

The structure for the assessment of the coronary vessels was the same as that used for invasive coronary angiography (ICA). The coronary vessels were thereby divided into 18 segments (121). By the use of a three-point scale (excellent, acceptable, not diagnostic) the evaluation of the segments was conducted by two radiologists with 10 and 20 years of experience in radiology. The readers were blinded to all scan and clinical parameters. For the assessment of image quality they both used individualized window settings, window width (WW) 800-1200 HU, window level (WL) 100-200 HU.

3.3.7 Statistics

Differences between IOCM and LOCM were analyzed using Student's unpaired *t* test. Differences in total number of hb faster than 80 hb/min and 100 hb/min, the number of patients with changes in heart rate interfering with the scan protocol defined before scanning, the number of diagnostic segments, and the number of segments affected by movement artifacts were analyzed using Fischer's exact test. Difference in image quality was tested using the Mann – Whitney U test. The relationship between the deviation in heart rate from the individual mean heart rate in the selected protocol and

the proportion of segments affected by movement artifacts was obtained by using linear regression analysis. To estimate the association between body size and the attenuation in aorta and LMCA , Pearson's correlation coefficient *r* was calculated for each of BW, BH, BMI, LBM, IBW and BSA. *P* values <0.05 were considered significant.

3.4 STUDY II

3.4.1 Patient preparation

BW was obtained in light clothing (underwear) using a medical balance (Soehnle professional, GMBH Company, Germany) and BH was obtained in the standing position without shoes using a dedicated wall-mounted ruler. An 18 gauge peripheral venous access was inserted into the right or left antecubital vein.

3.4.2 Scanning parameters and technique

All examinations were executed during apnea using a tube current of 120 kVp and automatic dose modulation, ranging from 100 mA to 700 mA. The scanning procedure included a three-phase protocol at a 64 x 0.625 mm detector collimation. The native phase was obtained with a noise index (NI) of 50 and a pitch of 1.375. The CM phases, late arterial phase (portal venous inflow phase) and the hepatic parenchymal phase, were conducted with NI 36 and pitch 0.984. Scan start for the CM phase was defined by using bolus tracking technique (smart prep), where the triggering ROI was placed in the thoracic aorta at the level of the aortic arch. Scan start was set to 20s post threshold value. All sampled data were reformatted to 5 mm thick slices with a 2.5 mm reconstruction overlap.

3.4.3 Intravenous contrast media technique

The study was carried out with the injection of two different CM, iodixanol 320 mg I/ml (Visipaque ®-320, GE Healthcare, Chalfont St. Giles, United Kingdom) or iomeprol 400 mg I/ml, (Iomeron®-400, Bracco Imaging SpA, Milan, Italy). The pre heated CM was filled into one of the power injector syringes (Medrad, Stellant Dual Head Injector, Pittsburgh, Pennsylvania, USA). For all participating patients a CM dose of 40 grams of iodine with a duration time of 25 s were used, e.g. 125 ml of iodixanol with injection rate of 5 ml/s or 100 ml of iomeprol at a rate of 4 ml/s. This resulted in an injected dose rate of 1.6 gram-iodine per second for both CM. The CM injection was followed by a 50 ml saline flush with injection rate corresponding to the CM injection.

3.4.4 Data analysis study

All images were evaluated using a dedicated workstation (Advantage work station, GE Healthcare, Milwaukee, Wisconsin, USA). A circular ROIs with a diameter of about 10 mm was used. The attenuation in aorta was obtained at the level of the liver hilum before CM administration (native phase) and during the late arterial phase. The attenuation of liver was obtained in the native and the hepatic parenchymal phase from ROIs placed in:

1) -central part of the liver

2) - liver 3 cm caudal to the hemidiaphragm

3) -liver 3 cm cranial to the caudal edge of the liver.

Care was taken to avoid any partial volume effects and not to include any visible vessels or areas with inhomogeneous attenuation in the liver. The contrast enhancement was calculated as the attenuation after contrast media subtracted with the attenuation in native phase. The measured values obtained at the three levels in the liver were finally averaged.

3.4.5 Statistics

Pearson's correlation coefficient *r* was calculated overall and for males and females separately for the association between hepatic and aortic enhancement, respectively, and the parameters BW, BH, BMI, LBM, IBW and BSA. We assessed differences for the overall data set in these correlations for BW versus any measures of body size with a higher correlation coefficient than BW by comparing squared unstandardized regression residuals from univariate linear regression analyses using the Wilcoxon signed-rank test. The Fisher r- to –z transformation was used to test differences in correlation between males and females. Mann-Whitney U-test and t-test for two independent samples were used to test for median and mean differences in aortic and hepatic enhancement of the two different CM, iodixanol and iomeprol. Linear regression was employed to adjust the differences in the enhancement of males and females and of the two different CM for differences in age, weight and height. All statistical analyses were conducted in SPSS release 18.0.1 (SPSS Inc, Chicago, U.S.). P-values <0.05 were considered significant.

4 MAIN RESULTS

Study I: There were no statistically significant differences between patients receiving IOCM or LOCM in terms of heart rate interfering with pre scan defined protocol. A greater number of arrhythmic heart beats was observed with use of LOCM in comparison to IOCM ($P<0.001$). There were no significant statistical differences in image quality between the two CM. The level of experienced heat sensation was significantly higher when using LOCM in comparison to when using IOCM ($P<0.05$), VAS = 36 mm and 18 mm.

Study II: None of the tested body size measures BH, BMI, LBM, IBW or BSA demonstrated any significantly better correlation in hepatic parenchymal or aortic late arterial phase CM enhancement than BW did. When adjusting for differences in weight, height, age and sex between the two groups there was a significantly stronger liver CM enhancement with iodixanol than that of iomeprol, (mean difference 6 HU, $P<0.01$).

5 RESULTS AND COMMENTS

5.1 Study I

5.1.1 Results

A total number of 100 patients referred for CCTA were divided into LOCM group, 32 male 18 female, mean age 63 (SD 7) and into a IOCM group, 31 male 19 female, mean age 64 years (SD 8).

The average numbers of hb needed to cover the whole heart was for LOCM group 4.75 hb (SD 1.14) and for IOCM 4.35 hb (SD 0.58 HB). The total numbers of hb was for LOCM group 199 hb and for IOCM group 184 hb.

During CCTA there were no significant (NS) differences between LOCM group and IOCM group in number of patients interfering with pre scanned defined protocol (31 vs 32). The mean variability in heart rate interfering with pre defined scanning protocol was for the LOCM group 4.7 hb per minute (hb/min) (SD 12) and for the IOCM group 2hb/min (SD 4.1) (NS).

Comparing differences in average heart rate during CCTA did not show any significant differences between LOCM and IOCM (64 vs 59.6). Same results were seen in comparing heart rate variability during CCTA, LOCM 4.4 hb/min (SD 10.9) and IOCM 1.4 hb/min (SD 3.4) (NS) (Table 6)

The results for comparing arrhythmic hb exceeding the defined level of 80 HB showed a significant higher incidence using LOCM 26 hb in comparison to IOCM 3 hb ($P<0.0001$). The same was for arrhythmic hb exceeding the defined level of 100 hb showed significant differences between LOCM group 15 hb and IOCM group 1 hb ($P<0.001$).

The analysis of the questionnaire for VAS (n=88) showed a significant higher level of experienced heat sensation in LOCM group (n=43) (VAS 36 mm) in comparison to IOCM group (n=45) (VAS 18 mm) ($P<0.05$) (Figure 13).

The image quality assessment showed NS differences in number of diagnostic segments (514 vs 492) or segments affected by movement artifacts (153 vs 167) between LOCM and IOCM groups. Analysis of the proportion of segments affected by movement artifacts and the deviation from pre defined scanning protocol showed a significant relationship ($r=0.29$, $P<0.01$).

Table 6. Differences in average heart rate during CCTA.

Parameter during CCTA	LOCM	IOCM
Increased heart rate (*n*)	21	16
Decreased heart rate (*n*)	14	12
Both increased and decreased (*n*)	4	0
Mean variance in heart rate (hb/min)	4.4 (SD 10.9)	1.4 (SD 3.4)
Total deviation in heart rate from the scan protocol (hb/min)	4.7 (SD 12.0)	2.0 (SD 4.1)

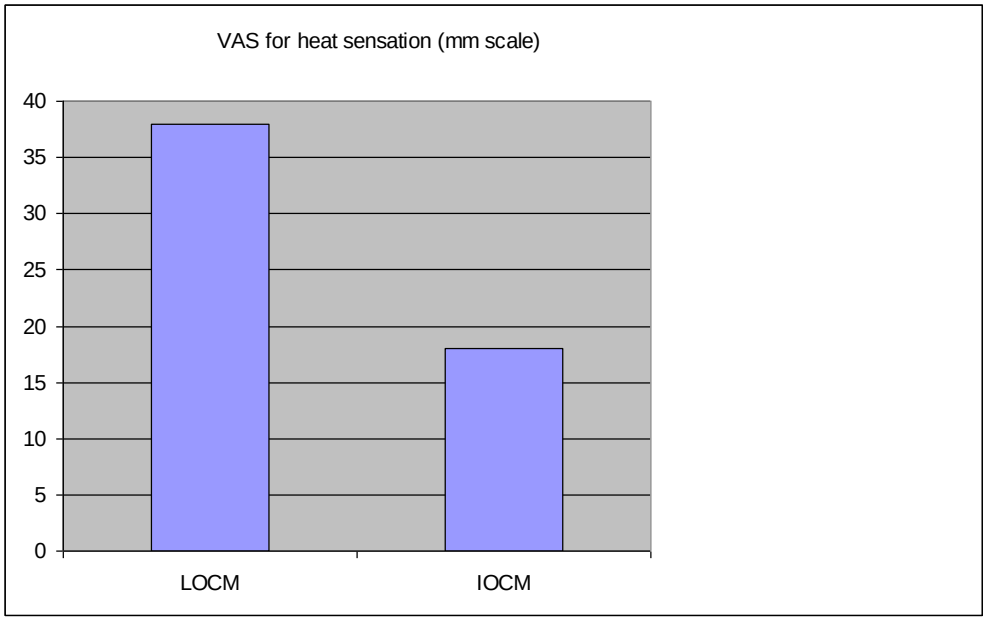


Figure 13. The difference in VAS between LOCM and IOCM in relationship to experienced heat sensation.

5.1.2 Comments

In our study the injected volume of CM was equal for LOCM and IOCM. However, because the concentration of LOCM (400 mgI/ml) was higher than that of IOCM (320 mgI/ml), the total amount of iodine was greater when injecting the LOCM iomeprol. This resulted in a difference of 5.6 gram between the two CM, which may be considered a limitation of our study. However, the alternative would have been to use different injection rates, which at that time point was considered difficult. Another potential limitation was the use of β-blockers. However, there was no difference between the two groups in the number of patients on prescription for β-blockers. Of the 100 examined patients in study I, 83 were on prescription of β-blockers (41 in LOCM group and 42 in IOCM group). In connection with the CCTA examination 5 of the otherwise untreated patients received intravenous β-blocker (3 in LOCM group and 2 in IOCM group).

5.2 Study II

5.2.1 Results

All studied body size parameters were statistically significantly negatively related to the CM enhancement in liver and aorta (Table 7, 8).

There was a wide inter patient variation in HU enhancement of liver and aorta; between 37 and 91 HU in the liver and between 125 and 452 HU in the aorta at late arterial phase (95% percentile range), aorta enhancement phase 93-404 HU (95% percentile range). In 11 patients the liver CM enhancement did not reach the level of 50 HU (Table 9).

When analyzing the CM enhancement in liver, three parameters showed a stronger influence on CM enhancement, BW (r = -0.64, Figure 14), BSA (r = -0.65) and LBM (r = -0.59) while BH, BMI and IBW showed weaker correlations (Table 7). The negative correlations ranged from -0.59 to -0.65 resulting in a r^2 of 0.35-0.42, i.e. 35-42% of the variability in liver enhancement was associated with differences in body size. The aortic evaluation showed that BSA and LBM had the strongest correlation to CM enhancement (r = -0.54, Figure 15) but the difference to that of BW (r = -0.51) was small and insignificant (p = 0.07 and p = 0.31, respectively; Table 8). Thus, for aortic enhancement body size explains about 25-30% of the variability.

When comparing the correlation between different body size measures and CM enhancement of males versus those of females similar results for liver and aorta were observed with the exception of BH and IBW where the female group showed weaker correlations. However, the differences in comparison to the male group did not differ significantly (liver: p = 0.16-0.18; aorta p =0.14 for both measures) (Table 7, 8).

Comparing the two CM, iodixanol and iomeprol, we found similar mean CM enhancement of the liver (65 HU versus 63 HU, p = 0.22). However, when adjusted for weight, height, age and sex, iodixanol caused significantly stronger liver enhancement than iomeprol (mean difference 6 HU, p < 0.01) (Table 10). There was no significant difference in aortic CM enhancement between the two CM, neither before (mean difference 233 HU versus 229 HU, p > 0.30) nor after adjustment for differences in weight, height, age and sex (mean CM enhancement difference 13 HU, p > 0.30).

Table 7. Pearson's correlation coefficient regarding hepatic enhancement in the parenchymal phase in relation to various body size measures.

Parameters	All (n=100)	Women (n=42)	Men (n=58)
Body weight (kg)	-0.64	-0.66	-0.57
Height (cm)	-0.45	-0.19	-0.46
Body mass index (kg/m^2)	-0.50	-0.57	-0.44
Lean body mass, James (kg)	-0.59	-0.63	-0.61
Ideal body weight (kg)	-0.44	-0.19	-0.46
Body surface area Mosteller (m^2)	-0.65	-0.67	-0.60

All correlation coefficients were statistically significant at the p<0.0001 level

Table 8. Pearson's correlation coefficient regarding aortic enhancement in late arterial phase in relation to various body size measures.

Parameters	**All (n=100)**	**Women (n=42)**	**Men (n=58)**
Body weight (kg)	-0.51	-0.38	-0.50
Height (cm)	-0.44	-0.15	-0.43
Body mass index (kg/m^2)	-0.35	-0.32	-0.37
Lean body weight, James (kg)	-0.54	-0.42	-0.54
Ideal body weight (kg)	-0.45	-0.15	-0.43
Body surface area Mosteller (m^2)	-0.54	-0.40	-0.53

All correlation coefficients were statistically significant at the p<0.0001 level

Table 9. Attenuation and contrast medium enhancement of the liver and aorta expressed in Hounsfield Units (HU). Median values with 2.5 – 97.5 percentiles.

Parameters	All (n = 100)	Females (n=42)	Males (n = 58)
Liver			
-native phase (HU)	57 (33-70)	60 (31-71)	56 (37-63)
-parenchymal phase (HU)	119 (83-152)	129 (83-153)	115 (84-143)
-enhancement (HU)	63 (37-91)	68 (44-92)	59 (36-87)
-enhancement <50 HU	n = 11	n = 2	n = 9
Aorta			
-native phase (HU)	37 (23-49)	39 (29-48)	35 (20-48)
-late arterial phase (HU)	252 (125-452)	305 (168-466)	231 (120-425)
-enhancement (HU)	217 (93-404)	265 (129-424)	188 (88-384)

Table 10. Hepatic and aortic enhancement (Hounsfield Units, HU) of iodixanol (320 mg I/mL) and iomeprol (400 mg I/mL), both injected at a dose of 40 grams of iodine and a dose rate of 1.6 gram iodine per second. Median values with 2.5 – 97.5 percentiles. The values shown have not been corrected for differences in sex and body parameters.

Parameters	Iodixanol (n=55)		Iomeprol (n=45)	
	Mean value	Median value (2.5 – 97.5 percentiles)	Mean value	Median value (2.5 – 97.5 percentiles)
Liver, parenchymal phase	65	65 (42-90)	63	59 (34-91)
Aorta, late arterial phase	233	232 (86-362)	229	199 (121-424)

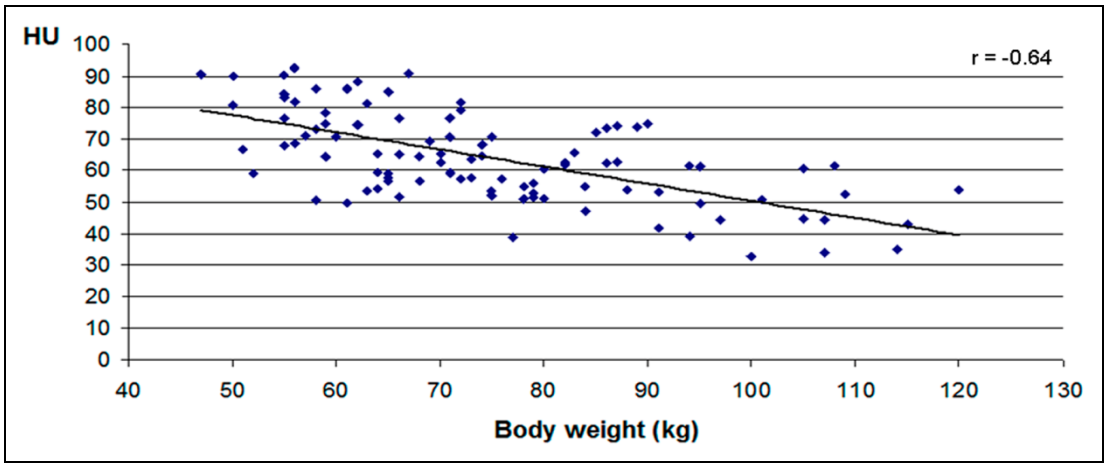


Figure 14. Liver parenchymal CM enhancement as a function of BW.

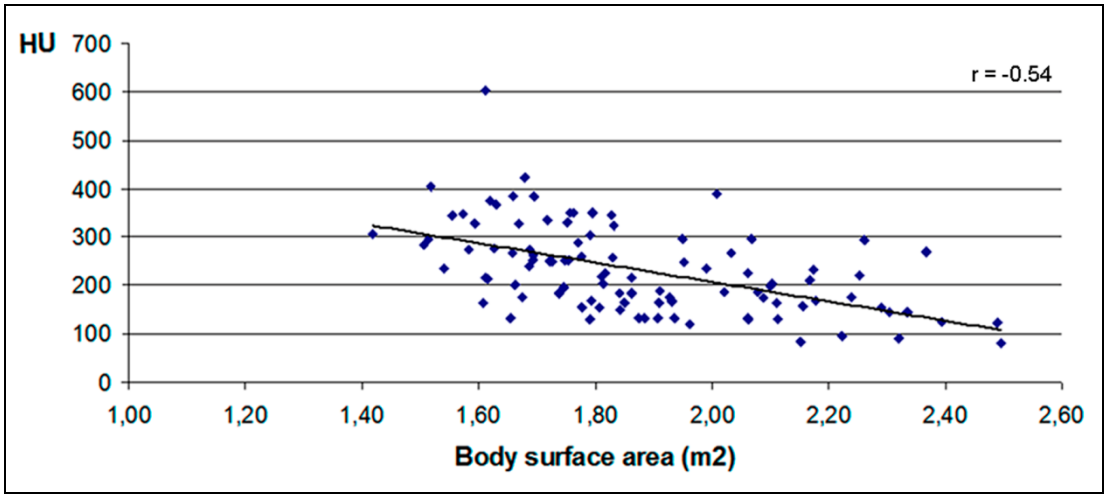


Figure 15. Aortic CM enhancement as a function of BSA.

5.2.2 Comments

About 35-42% of the CM enhancement of the liver observed in our study was associated to body size, expressed as BW, BSA or LBM. The corresponding association in aorta was 25-30%. IBW, BH, and BMI showed a weaker association. Apparently, not only body size affects HU-enhancement. One such parameter is cardiac output. To compensate for differences in cardiac out put bolus tracking (smart prep) technique was used. However, the delay between the threshold value (HU-value) and the scanning of aorta was 20s which might have influenced the result, especially for the aortic CM enhancement.

The CM enhancement of liver varied between 37 and 91 and for aorta between 93 and 404 HU. In 11 patients (9 males, 2 females) the CM enhancement of the liver did not reach the threshold value of 50 HU, which is considered to be the minimum CM enhancement for good diagnostic quality (111). This indicates that an insufficient amount of CM was administered to these patients (BW males 84-115kg, median 97 kg , females 107 and 114 kg) (Figure 16). There were also patients in the other end of the spectrum, in which the dosage of CM can be questioned due to a too high level of CM enhancement. This was more explicit among females, where 18/42 had a liver CM enhancement exceeding 70 HU in comparison to male group 16/58.

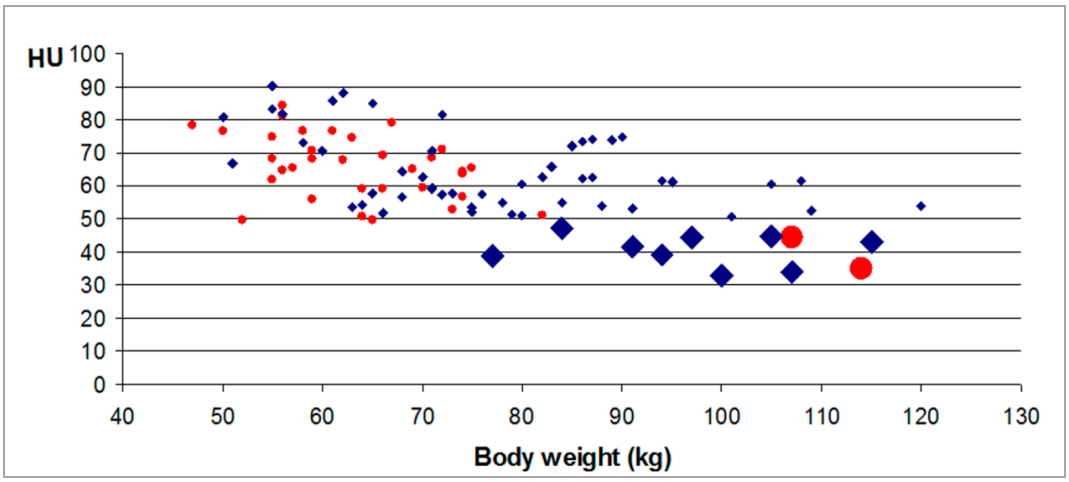


Figure 16. During liver pharenchymal phase 11 patients (9 males ♦ and 2 females ●) did not reach threshold of 50 HU enhancement.

6 DISCUSSION

6.1 Heart rate variability and heat sensation at CT coronary angiography: Low-osmolar versus iso-osmolar contrast media (study I)

The evaluation of the coronary vessels in our study using the method for retrospective gating with 64 row MDCT was challenging. The amount of hb necessary to cover the whole heart, ranged between 4-7 hb. The more hb needed, the higher is the risk of heart rate changes occurring during the acquisition, resulting in a poorer CCTA examination.

The ¨golden rule¨ for CCTA is a low and stable heart rhythm (84). More recently developed MDCT systems (e.g Siemens dual source, Somatom Definition Flash, Siemens Healthcare, Erlangen, Germany) have a better temporal resolution and coverage than previous MDCT systems. The new systems use so called high pitch scanning, which gives the possibility to exam the whole heart during one single heart beat (122).

In our study there were no statistically significant differences between LOCM and IOCM groups in number of patients interfering with pre defined scan protocol. However when analyzing arrhythmic hb alone and when analyzing heart rates exceeding 80 and 100 hb/min there were a significantly more arrhythmic hb when using the LOCM iomeprol than when using the IOCM iodixanol. The absence of any difference in number of hb interfering with the predefined scan protocol between LOCM and IOCM has been confirmed in a later study (123), but unfortunately that study did not analyze the frequency of arrhythmic hb.

A potential limitation of our study was that a larger amount of iodine was used in the LOCM group compared to that of the IOCM group. However, the two radiologists, who were blinded to which CM that was used, could not observe any significant difference in terms of image quality.

Patients in the LOCM group experienced a stronger heat sensation than those in the IOCM group (VAS 36 vs 18, P = <0.05). This complies with previous studies using LOCM and IOCM for CCTA (124). The discomfort of experiencing a heat sensation may affect the heart rate. This may affect CCTA performed on 64 row MDCT systems, because several hb are required to cover the whole heart. CCTA performed on more recent systems, which have a better temporal resolution and coverage, are probably less affected.

I order to optimize the 64 row CCTA there are specific needs that have to be fulfilled. The key point is to minimize all potential factors that may affect the CCTA quality. Such factors are; patient discomfort, placement of the IV peripheral catheter, placement of ECG leads, heart rate monitoring and quality of breathing instructions. The compliance from the patient is important, and so is also the patient selection

(e.g. extensively calcified plaques, arrhythmia and heart rate). The understanding of all these related factors makes the presence of well educated and skilled CT staff important (84).

6.2 Hepatic contrast medium enhancement at computed tomography and its correlation with various body size measures (study II)

Instead of the fixed dose paradigm (¨one dose fit's all¨) the use of a more individualized CM dosage approach has been suggested. By this approach a more uniform HU-enhancement regardless of BW has been achieved (58, 59).

In our study we evaluated 6 different calculations for the estimation of body size. It could be shown that BW, LBM and BSA had the strongest association to CM enhancement in liver and aorta, but that there was no significant difference in association strength among them. Therefore, these parameters would be most efficient to use when compensating CM dose for body size. In theory, if the CM dose had been adjusted for BW (mgI/kg BW) approximately 40% of the variation in liver CM enhancement could have been avoided.

Previous studies, made in Japan, have observed that when adjusting for LBM a lower inter patient variability of hepatic CM enhancement was achieved compared to that when BW was used (62, 65). However, their analyses of LBM were based on percent body fat measured using a body fat monitor, while our measurement of LBM was based on an analysis of height and weight in accordance to the equation by James. Other studies using James's equation to calculate LBM have obtained results consistent with ours (65). In daily clinical practice the use of a body fat monitor to calculate LBM may seem impractical, but the results of the two Japanese studies imply that James's equation could be improved.

A CM enhancement of at least 50 HU has been advocated to be the threshold for sufficient diagnostic accuracy when imaging the liver in the parenchymal phase (111). In that study, the calculated dose to reach that level was 521 mg I/kg. When analyzing the data of our study that dose could be verified; the average BW of the patients with a CM enhancement ranging 50 to 70 HU was 76 kg, equivalent to 526 mg I/kg. Based on the CM enhancement of the liver, some of the individuals in our study received an unnecessarily high CM dose (40gI in a 50kg individual is equal to 800mgI/kg BW).

Ichikawa et al. showed the optimal peak enhancement of the liver occurs after 25s of injection (69). However, if the dose is adjusted for body size, for instance BW, the required volume will vary between the patients. In order to inject the total amount of CM until that time the injection rate has to be varied among the patients, i.e. a fixed injection time is necessary.

As described in the background section, blood volume is related to body size, but there is great inter individual variation. For example, the low vascularization of fat tissue makes an obese person to have a smaller blood volume compared to that of a muscular person with the same BW. This will affect the CM enhancement (56, 57, 58). Thus, there is a potential risk in over dosing obese individuals when CM dosages are based on BW only. To reduce the over dosing problem in obese patients the introduction of a maximal dosage BW may be a solution.

When differences associated with gender and body size parameters had been adjusted for it was apparent that iodixanol caused a significantly stronger CM enhancement in the liver in comparison to iomeprol ($p<0.01$). The most plausible explanation is the

high osmolality of iomeprol. When diffusing out to the extracellular space of the liver parenchyma the hypertonic iomeprol may cause a rapid diffusion of water from the intra- to the extracellular space. This would lead to a dilution of the CM, resulting in the observed lower CM enhancement. An observed greater diffusion of fluid caused by hypertonic CM from the capillary bed into the extracellular space by iomeprol might be of importance when evaluating patients with edema.

6.3 Discussion synthesis

A significant relationship between CM enhancement in liver and aorta was observed for all studied body size parameters in study II. It might be discussed whether these parameters also affected the patients in study I. For that reason we retrospectively applied the same method as in study II on the HU measurements in aorta and left main coronary artery (LMCA). However, no native series (base line) were collected during study I, which implies that only the actual HU values could be studied. Due to CM timing errors two patients were excluded, resulting in 98 individual measurements.

The aortic HU values were obtained at the level of the origin of LMCA. The largest possible circular ROI was applied, carefully avoiding calcifications.

The results showed a significant relationship between HU values in aorta and LMCA for all measured body size parameters (Table 11, Figure 17). BSA and BW had the best correlation to the attenuation (BSA r= -0.50 and -0.49) (BW r= -0.45 and -0.46) which is in accordance with findings by Yanaga et al. (71).

Table 11. Pearson's correlation coefficient regarding attenuation in aorta and LMCA in relation to the body size measures.

Parameters	Aorta (n=98)	LMCA (n=98)
Body weight (kg)	-0.45	-0.46
Height (cm)	-0.47	-0.40
Body mass index (kg/m^2)	-0.19	-0.26
Lean body mass, James (kg)	-0.36	-0.34
Ideal body weight (kg)	-0.41	-0.36
Body surface area Mosteller (m^2)	-0.50	-0.49

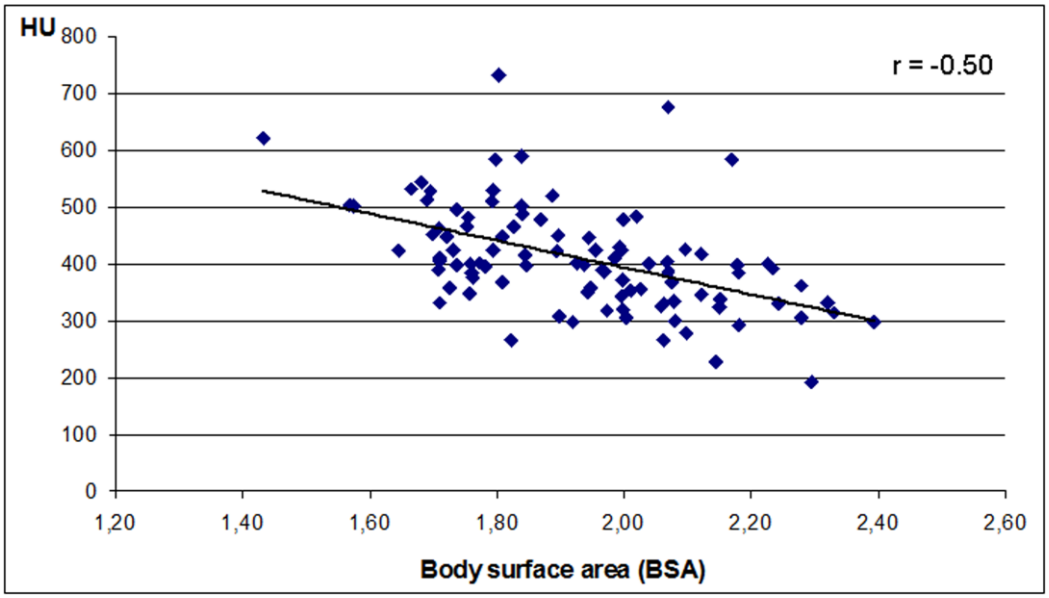


Figure 17. Attenuation in aorta as a function of BSA in patients undergoing CCTA.

7 CONCLUSIONS AND FINAL REMARKS

Study I:
There was no difference between the LOCM iomeprol or the IOCM iodixanol in number of patients deviating in heart rate from predefined heart rate protocol. Using the same volume of CM, but different total amount of iodine, did not affect the image quality assessment. When analyzing the total number of irregular hb exceeding 80 and 100 hb/min, there was a greater frequency of irregular hb in the LOCM group ($p<0.001$). LOCM was associated with a higher level of experienced heat sensation than IOCM ($p<0.05$). The results indicate that the IOCM iodixanol is more recommendable than the use of the LOCM iomeprol when performing retrospectively gated CCTA on a 64 row CT.

Study II:
The equations for BW, LBM and BSA showed the best correlation to CM-enhancement in liver and aorta in comparison to BH, BMI and IBW. To achieve a consistent hepatic enhancement, CM dose may simply be adjusted to body weight instead of using more complicated calculated parameters based on both weight and height. When adjusting for differences in weight, height, age and sex between the two groups there was a significantly stronger liver CM enhancement with iodixanol than that of iomeprol (mean difference 6 HU, $p < 0.01$).

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