Influence of iodinated contrast agents on heart rate variation and diagnostic image quality during CT angiography of the coronary arteries

Original Manuscript

Advances in knowledge

1. Contrast induced heart rate increase and heart rate variability depends on contrast material used for coronary CT angiographies
2. The lower increase and variability of contrast induced heart rate during coronary CT angiography using iodixanol led to an improved image quality on segment and on patient level as compared to coronary CT angiographies performed during the administration of iomeprol.

Implications for Patient Care

1. The image quality at coronary CT angiography can be positively influenced by using dimeric iodixanol due to the decreased heart rate variability as compared to monomeric iomeprol.
2. Patient discomfort as described as heat sensation during the injection of iodinated contrast-material for coronary CT angiographies can be reduced by using the iso-osmolar contrast agent iodixanol

Summary statement:

The dimeric iodixanol showed a later-occurring and significantly lower heart rate increase, compared to the monomeric iomeprol. This was directly related to increased patient comfort, and to increased image quality when iodixanol was used.

Abstract and Keywords

Purpose To assess the influence of different contrast agents on heart rate variability and image quality during coronary computed tomography angiography (CCTA).

Materials and Methods: There were 205 patients (94 women) referred for CCTA to exclude CAD, with a baseline heart rate below 70, who were consecutively enrolled in this study. CCTA was performed after randomization to either iodixanol (n=100) or iomeprol administration. Patients were divided into three groups according to their body weight. All patients within same body weight group received the same amount of iodine per second. Heart rates were recorded with a mobile heart rate monitor before, during, and after contrast media administration. Contrast enhancement was evaluated at four predefined anatomical regions and image quality was assessed on segment level.

Results: While both contrast agents raised the mean heart rate within 60 seconds after injection, iomeprol elevates the heart rate earlier and to higher levels, with a peak heart rate change of 14 bpm (iodixanol, 7 bpm). Thirty-five seconds after the start of contrast administration, iomeprol was found to induce significantly higher heart rate changes (increases) when compared to iodixanol. In the group of patients with a body weight between 55 and 100 kg n=175), the differences in heart rate became significant within 17 seconds after the start of contrast injection. There was no difference in arterial contrast enhancement between the two agents.

Conclusion Iodixanol showed significantly less influence on heart rate during CCTA of the coronary arteries combined with better image quality when compared to iomeprol. Thus, the differences in contrast-media induced heart rate variability turned out to be of clinical relevance and the use of Iodixanol seems to be advantageous for CCTA.

Keywords: heart rate, contrast agent, image quality, CCTA, dimeric

Introduction

The technical capabilities of non-invasive Computed Tomography (CT) angiography of the coronary arteries (CCTA) have improved continuously over the last decade. Thus, CT angiography of the coronary arteries was established as an important non-invasive tool in the management of patients suspected of or suffering from coronary artery disease (CAD). Following the updated recommendations for the appropriate use of CT angiography as published previously [1], CCTA arteries is mainly indicated in patients with typical or atypical chest pain and low-to-intermediate pre-test probability [2]. In this group of patients, non-invasive exclusion of CAD with CCTA is possible, with a very high negative predictive value [3]. It is obvious that this high negative predictive value can be obtained only in patients with satisfactory image quality that enables the assessment of all coronary artery segments.

In case of insufficient diagnostic image quality, CAD cannot be ruled out in all segments, and further tests would be required. Thus, excellent image quality is of the utmost importance for the clinical usefulness of CCTA [4]. The relation between image quality and heart rate has already been described extensively [5-7]. The higher the heart rate is, the shorter the diastole will be, and consequently, the less time the more-or-less motion-free period of the coronaries will last. In addition, every change in heart rate during scanning can deteriorate the image quality. Despite the tremendous technical improvements in CT scanners over the last few years, with exciting improvements in temporal resolution, heart rate remains an important and sometimes limiting factor for the image quality of CCTA.

To reduce the heart rate during CT scanning, beta-blockers are widely used, administered either orally (at least one hour before the examination) or intravenously (on the CT table). However, as recently shown by Fleur de Graaf, in a substantial number of patients, beta blockers are contraindicated or cannot be administered at the dose really required, and the target heart rate (below 70 beats per minute (bpm)) is not reached [8]. Thus, a relevant

number of patients are scanned at heart rates that are too high, with the inherent risk of limited diagnostic image quality.

Iso-osmolar Visipaque 320 has recently been shown to reduce heart rate variations during CCTA in a small patient population, compared to the hyperosmolar Iomeron 400 [9]. The explanation for that could be differences in the molecular structure or physicochemical properties of the agents, leading to a different influence on electrophysiological parameters.

It has also been shown that discomfort (feeling of heat, cold, and/or pain at the injection site) is lower when using an iso-osmolar agent compared to agents that are hyperosmolar to blood, which has been primarily attributed to osmotoxicity [10-13].

The aim of this prospective, randomized, blinded study was to assess the influence of the two contrast agents on heart rate variations, and consequently, on image quality, in a large and homogenous patient population.

Methods

Study Design

This study was designed as a single-center, randomized, prospective, and blinded study. The investigators were blinded to the contrast agent (CA) used. CCTA and acquisition of the heart rate were performed by an independent technologist who was not involved in data management and/or analysis. This prospective study was approved by the Institutional Review Board (N° 260/2011) and complies with the Declaration of Helsinki.

Study population

Patients referred for CCTA to rule out coronary artery disease (CAD) were invited to participate in this study. After an oral explanation of the content of the present study, written, informed consent was obtained from all patients. After obtaining consent, patients were randomized into two groups to receive either iodixanol or iomeprol during CCTA. The prerequisites for inclusion were age > 18 and the presence of a sinus rhythm. Exclusion criteria included a history of coronary stent placement, coronary bypass graft surgery or heart transplantation, history of multiple myeloma, impaired renal function (eGFR < 60 ml/min), untreated hyperthyreosis, as well as a history of allergic reaction to contrast agents. The randomization was accomplished using QuickCalcs (GraphPad, USA).

Based on the results from an internal, as yet unpublished, retrospective analysis of previously investigated patients, the sample size was calculated as follows. A sample size of 193 would have had 80% power to detect a mean difference of 2 bpm, assuming a standard deviation of 7 bpm (according to the previously assessed data) using a two-group t-test with a 0.05 two-sided significance level. To compensate for a drop-out rate of up to 5% of the patients, 10 additional patients would have to be included in each group. Thus, the total

number of included patients would have to be at least 203. Altogether, 207 patients (mean age: 57.5 +- 11.2 years; range: 29 – 86 years; 95 women, mean age: 59.3 +- 10.6 years; 112 men, mean age: 56.0 +- 11.5 years), with heart rates below 70 bpm at baseline (see below), were included in this study; 101 patients were randomized to receive iodixanol and 106 to receive iomeprol during CCTA. The per-protocol population was defined as all patients whose CCTA and heart rate assessment could be finished as planned.

Examination Technique

CCTA was performed on a dual-source CT scanner (Somatom Definition Flash, Siemens Health Care, Forchheim, Germany) with a detector collimation of 2x64x0.6 mm and applying a z-flying focus technique resulting in an effective collimation of 2x128x0.6 mm. Axial images were reconstructed with a 0.6 mm slice thickness and a 0.4 mm recon increment, using a medium sharp convolution kernel (B26f). In general, a prospective ECG triggering technique was used for all CT examinations. However, the specific scan mode was selected according to the height and variability of the heart rate at baseline (see below). For a heart rate below 60 bpm, a high-pitch spiral scan protocol (Flash mode) was selected; in the other patients, an adaptive step-and-shoot technique with a widened acquisition window (padding) was applied to allow for the assessment of diastole and systole as well and to remain stable against pulsation artifacts. The padding window ranged from 35 – 80% of the RR interval. The scan was started automatically when the predefined threshold of 150 Hounsfield units (HU), with the Flash mode technique, and 100 HU, with the step-and shoot technique, was reached in the descending aorta. Only patients with a heart-rate up to 70 bpm were included in this evaluation.

Administration of Contrast Material

Patients within both groups were subdivided according to their body weight into three body weight groups (<55 kg, 55 – 100 kg, >100 kg). Based on weight, the total amount of iodine was defined for each group, which determined the other parameters for contrast injection. The acquisition time, the injection duration, and thus, the injection speed, were defined, ensuring the same iodine delivery rate within every body weight class for both contrast agents (see Table 1). Patients who weighed below 55 kg received an iodine dose of 28 g, with a delivery rate of 1.76 g per second, patients between 55 kg and 100 kg received a total dose of 32 g, with a flow of 2 g per second, and patients above 100 kg received 36 g at a rate of 2.24 g per second. Therefore, as shown in Table 1, the amount of contrast agent used and flow parameters were different between the two groups, but ultimately, the three groups had the same iodine delivery rate, independent of the iodine concentration of the contrast agent used. All contrast injections were performed using an automatic power injector (Accutron CT-D; Medtron AG, Germany) at the given delivery rates and doses, and were followed by a saline flush.

Mark for Table 1

Heart Rate Evaluation

The heart rate of each patient was assessed with a heart-rate monitor (Polar, RS800 CX, NY, USA). Using this system, the duration of each RR-interval in milliseconds was recorded for predefined periods of time, as detailed in the following. First, heart rate was monitored for 60 seconds before the start of contrast agent injection during the acquisition of the Ca-scoring scan. The mean heart rate during this one-minute scan was defined as the baseline heart rate. This baseline heart rate was used to select the scan parameters, as described above. The second measurement was initiated simultaneously with the start of the contrast injection and lasted for 360 seconds. Given these data, both the changes in heart rate and the variability of

the RR-interval duration before, during, and after the injection of contrast agent could be assessed independent of the scan mode applied.

Assessment of Sensations

To assess possible sensations and/or discomfort caused by the contrast injection, patients were interviewed about the presence of cold, pain, and heat sensations during contrast agent injection using a numerical rating scale from zero to 10 within 30 minutes after the end of the CT acquisition. Zero was defined as no sensation and ten as the strongest sensation imaginable.

Evaluation of Contrast Enhancement

The arterial intravascular contrast enhancement was measured by one reader blinded to the contrast material used in all patients, at the level of four predefined anatomical regions. A circular region of interest (ROI), with an area of about 1 cm^2, was placed in the left atrium and left ventricle, with an area of about 0.4 cm^2 in the sinus valsalvae, and about 0.05 cm^2 in the LCA for each patient (figure 1). The measured contrast enhancement values (HUves) in Hounsfield units (HU) were used to calculate the contrast-to-noise ratio (CNR) and signal-to-noise ratio (SNR). The equations applied for the calculation of CNR and SNR have been described previously [14] and are detailed below (Equation 1 and 2). The standard deviation of background noise (SDBN) was obtained from the standard deviation of the enhancement value of surrounding air (average of two measured values with an area of about 1 cm^2), and the muscle enhancement value (HUmusc) from the back muscle, as measured at the level of the intraarterial measurements, with an area of about 1 cm^2.

Mark for Equation 1 and 2

Rating of Image Quality

The image quality was evaluated by one independent reader, blinded to the contrast agent used. Overall image quality was described on a scale from zero to four (0: not assessable; 1: poor quality, more than 50% of segments not assessable; 2: suboptimal quality, diagnosis hampered; 3: good quality, diagnosis possible without limitations; 4: excellent quality, no limitations). Furthermore, the image quality was rated for each coronary artery segment following the 15-segment model proposed by the American Heart Association (AHA) [15] (fig. 2).

Statistics

All analyses were performed using MATLAB (Matlab 7.14.0, Release 2012a, Mathworks Inc., Sherborn, MA, USA) and the Statistical Package for the Social Sciences, Version 20.0 (SPSS, Chicago, Illinois). The alpha level for all tests was set at $p=0.05$ (two sided) with a 95% confidence interval.

Demographic data were analyzed and evaluated for significant differences between the iodixanol group and the iomeprol group. Differences in weight, body mass index (BMI), and age were tested with an unpaired t-test and gender balance was tested with a chi-square test.

For the data evaluation, the originally recorded discrete time series of RR intervals was first converted into a continuous function by linear interpolation, which was then sampled in one-second intervals to yield a regular, periodic series of RR interval values (in ms units); this series was the basis for the consecutive statistical analysis. In the following discussion and graphical representation of our results, the RR intervals are usually converted into heart-beat rates (in bpm units) to allow direct comparison with the related literature.

The average heart rate (in bpm) of the initial measurement phase (60 seconds, before CA administration) was defined as the patient's resting heart rate (baseline). Heart rate

changes after CA administration, defined as the deviations from the baseline, were determined once per second over a total of 50 seconds for each patient, and the two groups were then tested for significant differences.

To evaluate changes in the variability of the RR interval duration during CA administration, two parameters were assessed: the standard deviation of all normal RR intervals (SDNN), which covers long-term RR variability; and the Root Mean Square of the Successive Differences (RMSSD), which covers short-term RR variability [16].

SDNN was calculated as shown in the following equation (Equation 3).

Mark for Equation 3

In equation 3, N represents the total number of RR intervals, RR the duration of the RR intervals in ms, and $\overline{RR}$ the arithmetic mean of all RR intervals in ms.

RMSSD was calculated as shown in equation 4.

Mark for Equation 4

N represents the total number of RR intervals and RR the RR interval duration in ms.

The parameters SDNN and RMSSD were calculated for each patient individually using the first measurement ("baseline") and the first 60 seconds of the second measurement (during contrast injection), respectively. Subsequently, the difference between these measurements was used to eliminate individual patient RR variability. Results were tested for significant differences between the two CA groups using a Mann-Whitney U test.

The used tube voltage and examination protocol for CCTA were recorded and tested for differences in distribution between the two contrast agent groups using a chi-square test.

The HU values gathered for the four anatomical regions (left atrium, left ventricle, sinus valsalvae, and left main), as well as the calculated values for SNR and CNR, were tested for significant differences among the two CA groups using an unpaired t-test.

The assessed calcium scores (Agatston score) were classified as suggested by Rumberger et al. [17] (1: 0; 2: 0-10; 3: 11-100; 4: 101-400; 5: >400) and tested by the means of a Mann-Whitney U test for significant differences between the two agents. Overall image quality testing to compare the two CA groups was assessed using a Mann-Whitney U test. Furthermore, the image quality of the 15 segments was analyzed individually. Therefore, the number of segments per rating unit for each contrast agent was calculated and tested for significant differences between the two contrast agents using a Mann-Whitney U test. In addition, the average rating of all segments per patient of the per-protocol population was submitted to Mann-Whitney U test for comparison between the two CA. Additionally, segments were grouped according to the supplying artery (right coronary artery (RCA), left anterior descending (LAD), circumflex artery (CX) and tested for significant differences using a Mann-Whitney U test.

The gathered values for the sensations of heat, cold, and pain for both CAs were compared using a Mann-Whitney U test.

In addition, heart rate evaluation was also performed selectively for the mid-weight group (55 – 100 kg).

Results

Two patients (one receiving iodixanol, one receiving iomeprol) of the 207 patients included in this trial had to be excluded from further evaluation due to a technical problem in heart rate assessment, and a lack of data about the heart rate during scanning. For the remaining 205 patients, the specified per-protocol population data about heart rate were available, and assessment of contrast enhancement and image quality was possible. In one patient (iodixanol), the sensation evaluation form could not be obtained. Thus, a total of 205 patients (iodixanol: 100, iomeprol: 105) could be included in the evaluation of heart rate changes (per-protocol population), and the examination of image quality and contrast enhancement, and 204 in the evaluation of assessed sensations. No adverse events or complications occurred during the contrast injection. However, three patients had to be treated some minutes after the contrast administration with intravenous antihistaminic drugs due to an adverse reaction (one receiving iodixanol, two receiving iomeprol). Despite these adverse reactions after the examination, image and data acquisition could be performed and finished as planned.

The distribution of body weight groups among the per-protocol population was as follows: five patients presented with a body weight below 55 kg, (three iodixanol; two iomeprol); 175 patients were in the mid-weight group (86 iodixanol; 89 iomeprol); and another 25 had a body weight above 100 kg (11 iodixanol; 14 iomeprol). There was neither a gender distribution difference ($p > 0.05$) among the iodixanol group (49 women, 51 men) and the iomeprol group (45 women, 60 men), nor any difference in average age (iodixanol: 56.2 +- 11.5 years; iomeprol 58.6+-10.9 years; $p > 0.05$). Furthermore, the difference in average body weight (iodixanol: 78.6+-15.1; iomeprol 81.7+-16.6; $p > 0.05$) and BMI (iodixanol: 26.5+-4.3; iomeprol 27.1+-4.4; $p > 0.05$) was not significant between the two groups.

Heart rate

The average resting heart rate ("baseline") for the per-protocol population in the iodixanol group was 59.7 bpm, and for the iomeprol group, 58.5 bpm. For the mid-weight patients, it was 59.4 bpm in the iodixanol group and 58.5 bpm in the iomeprol group. These differences were not statistically significant.

As shown in Figure 1 for the per-protocol population within both study groups, heart rate increased after contrast injection, compared to baseline. There were differences in the maximal heart rate deviation between the two groups, as well as in the delay between the start of injection and attainment of the maximal heart rate. Thirty-five seconds after the start of injection, the difference in heart rate deviation from baseline became significant between the two groups ($p = 0.0115$).

Mark for Figure 1

In the mid-weight subgroup, this difference became significant more rapidly after the start of the injection, at 17 sec ($p = 0.0241$). The iodixanol group also showed, in this subgroup, a heart rate drop below baseline during the breath-hold maneuver (around 18 to 28 seconds after the start of the injection) (Figure 2).

Mark for Figure 2

The SDNN (long-term variation of the RR interval) was significantly higher in patients who received iomeprol compared to iodixanol (iodixanol: 68.6 ms; iomeprol: 93.1 ms; $p = 0.0017$). Differences in the RMSSD (short-term variation of the RR interval) were found to be not significant among the iodixanol and iomeprol group (iodixanol: 40.9 ms; iomeprol: 47.1 ms; $p > 0.05$). In the mid weight subgroup, the SDNN differed significantly (iodixanol: 68.1 ms; iomeprol: 90.7 ms; $p = 0.0013$), but, for the RMSSD, no difference was found (iodixanol: 40.9 ms; iomeprol: 44.8 ms; $p > 0.05$).

Patient discomfort

The subjective rating of cold and/or pain sensation of the patients (n=204) showed no significant differences between the two groups ($p > 0.05$). The median rating of heat sensation on the NRS was 7 after receiving iomeprol, compared to 5 after iodixanol. This difference showed statistical significance ($p=0.022$). In Figure 3, this difference can be seen in a boxplot. In the analysis for each rating unit individually, a clear difference was found in the percentage of patients who had given a rating of '10' (iodixanol: 3%, iomeprol 17.1%).

Mark for Figure 3

Contrast enhancement

The distribution of the tube voltage used showed no significant difference (n=204, $p>0.05$), although, in the iodixanol group, fewer patients (three patients) were scanned at a tube voltage of 140 kV, compared to the iomeprol group (nine patients) (Table 2). In one patient, the data about the tube voltage could not be obtained due to a missing patient protocol.

Mark for Table 2

The different examination protocols used (flash-mode or step-and-shoot mode) showed an even distribution (iodixanol: 26 flash, 74 step-and-shoot; iomeprol: 35 flash, 70 step-and-shoot; $p>0.05$).

The level of arterial enhancement showed no significant difference ($p>0.05$) for any of the four anatomical regions. The mean HU values at the sinus valsalvae level were the highest out of all four regions, with 441.4 for the iodixanol group and 424.2 for iomeprol. In SNR and CNR, there was also no significant difference ($p>0.05$). Table 3 shows the assessed values for both contrast agents for the per-protocol population.

Mark for Table 3

Image quality

No difference was found in the calcium score rating ($p>0.05$) among the two contrast agent groups. The mean Agatston score was comparable between the two groups. The assessment of subjective image quality demonstrated significant differences in overall image quality (iodixanol: 3.59 +- 0.67, iomeprol: 3.36 +- 0.77, $p=0.018$). Using iodixanol, 68.0% of the CCTA examinations were rated with 'excellent image quality,' with 51.4% rated excellent when using iomeprol. Table 4 shows the number of segments for each rating unit separately. Altogether, 235 segments could not be rated due to anatomical variations (iodixanol: 112; iomeprol: 123).

Mark for Table 4

On a segment basis, significantly more segments were rated with 'excellent image quality' when using iodixanol (73.8%) compared to iomeprol (62.7%) ($p=0.016$). In patients who received iodixanol, all segments could be assessed, whereas, in the iomeprol group, 0.9% were not assessable (13 segments from four different patients) ($p=0.049$). The mean of the average rating of all segments per patient differed significantly between the two contrast agents (iodixanol: 3.68 +- 0.47, iomeprol: 3.50 +- 0.61, $p=0.015$). Table 5 shows the average rating for each segment group (RCA, LAD, CX). In all three segment groups, the image quality was rated as better when using iodixanol ($p < 0.001$). For both contrast agents, the average image rating was lowest for the RCA (iodixanol: 3.5, iomeprol 3.3), and highest for the LAD (iodixanol: 3.8, iomeprol 3.6).

Mark for Table 5

Discussion

The present study has shown the advantages of using dimeric contrast agents for CT angiographies of the coronary arteries. The heart rate raise and variability could be decreased leading to an improved image quality and patient comfort. The study demonstrated the importance of choosing the appropriate contrast agent for improving outcome of CT angiographies of the coronary arteries. The negative correlation between high heart rate and image quality has been well known since the first clinical introduction of CT angiography of the coronary arteries [6]. Higher heart rates or arrhythmias are the most common cause for image quality deterioration. Despite fundamental technical improvements in hard- and software, including tremendous improvements in the temporal resolution of modern state-of-the-art CT scanners, heart rate remains an important factor for image quality. This importance is underlined by the fact that, even in recently published studies assessing the clinical value and clinical use of CT angiography of the coronary arteries, only patients with low heart rates were included, even if modern, ultrafast scanners were used [18, 19]. A heart rate below 65 to 70 bpm – depending on the temporal resolution of the scanner – is currently defined as the target heart rate for CT angiographies of the coronary arteries. To reduce the risk of limited diagnostic image quality due to pulsation artifacts, the use of beta-blockers for heart rate control is well established and recommended [20]. However, it has been shown recently that, in a relevant number of patients undergoing CT angiographies of the coronary arteries, heart rate control by administration of a beta-blocker is either not possible or not sufficient. As a result, a number of patients must be scanned at heart rates above the target heart rate [8, 21]. Therefore, additional methods for optimization of the heart rate are needed.

It has been reported recently that iodinated contrast agents increase the heart rate [22]. In addition, differences in the contrast-material-induced heart rate increase, depending on the contrast agent used, have been published [9, 23, 24]. Even for both the agents used in the present

study, iodixanol and iomeprol, differences in heart rates during CT angiographies of the coronary arteries have already been reported [9, 23, 24]. Differences in contrast-material-induced heart rate changes between these two agents could possibly be due to differences in the structure of these agents and to differences in the osmolarity [25]. However, the above-mentioned reports failed to definitively demonstrate the presence or absence of any significant difference between the two agents with regard to heart rate influence. One reason for the lack of clear results from these studies might be the fact that these studies were underpowered. Furthermore, the time of heart rate assessment was limited to the acquisition time, allowing only CT scanner-specific conclusions, since acquisition time may vary between different scanners and scan modes.

In the present study, which includes a rather large number of patients, we found a significant difference between the heart rate reaction after monomeric iomeprol and dimeric iodixanol. The maximal heart rate deviation from baseline, and the time to reach this maximal heart rate after contrast injection, was higher and occurred earlier in patients who received iomeprol compared to those who received iodixanol. This is of importance, since a delayed and limited change in heart rate could avoid pulsation artifacts caused by heart rate variations. In addition, in patients who received iomeprol, the long-term variability (SDNN) was higher than that in patients who received iodixanol, which was likely linked to the higher heart rate increase caused by iomeprol. In the short-term, there was no difference in heart rate variability, meaning that the variability of the duration of successive RR intervals was comparable between the two contrast agents.

To assess whether the differences in heart rate changes between the two groups had any influence on image quality, and were not merely more theoretical differences, image

quality was assessed and compared between the two groups. Although scanners with high temporal resolution and advanced protocols were used, and although only patients with baseline heart-rates below 70 were included, image quality was significantly lower in patients who received the monomeric iomeprol. The number of non-assessable segments was higher, and the number of segments rated to be of excellent image quality was lower in the iomeprol group. Since it is obvious that one single patient with severe artifacts could contribute up to 15 segments of limited image quality, image quality was also assessed on a per-patient basis. Even when comparing this parameter between the two groups, the iodixanol group showed a significantly better image quality than the iomeprol group. However, many additional factors besides heart rate and heart rate variability could influence the image quality and diagnostic accuracy of cardiac CT scans. Distribution among the two groups was also assessed for Ca-scores according to the classification introduced by Rumberger [17], and for the distribution of BMI, as well as for the selected kV settings. No significant differences were found between the two groups regarding these factors. Thus, it could be concluded that there should be a correlation between differences in heart rate elevation and variability, and the differences in image quality on a per-segment and on a per-patient level. These differences in image quality confirm the clinical impact of the changes in heart rate induced by the contrast material. The selection of contrast agent seems to be another factor that influences the image quality during CT angiographies of the coronary arteries, with beneficial effects of dimeric iodixanol.

Since two contrast agents with different iodine content were compared in this trial, any possible difference in contrast enhancement, as represented by CNR and SNR values, was also assessed. To obtain full comparability, contrast administrations in each body weight group were performed with the same iodine delivery rate (g iodine per second), independent of the contrast agent. Thus, direct comparability of the arterial enhancement was possible, and a comparison of the influence of contrast material on arterial enhancement levels, and on

CNR and SNR calculations, could be performed. The arterial enhancement at all four predefined anatomical levels, as well as the CNR and SNR values, were shown to be slightly higher in the iodixanol group. Although these differences were not statistically significant, these results demonstrate that the use of a contrast agent with lower iodine concentration has no negative influence on arterial contrast enhancement during CT angiographies of the coronary arteries if the injection protocol is adapted so that the iodine delivery rate is the same.

Previous studies [9, 11] have shown differences in heat sensation (stronger sensation of heat when using iomeprol), but, in these studies, different total iodine doses were applied. Our study confirmed these findings. Incidences of heat sensations were significantly greater and more severe after the injection of iomeprol, compared to iodixanol, despite higher flow in the iodixanol group. The reason for higher discomfort rates of hyperosmolar CA compared to isosmolar iodixanol after both intravenous and intraarterial applications is mainly attributable to the differences in osmolality[26, 27]. Another possible explanation for this difference could be the different molecular structure of these agents. It can be hypothesized that the higher osmolarity could be responsible for the higher heat sensation.

The results of the present study differ from previously published studies that assessed heart rate changes and variability during CCTA [9, 23, 24]. There might be several reasons and explanations for these differences. First, our sample size was considerably larger, and of sufficient power, after careful sample size calculation. In addition, the assessment of heart rate in the previously published studies was for a shorter period of time (during the CT scan) and not linked to the start of the contrast agent injection. Another limitation was the different iodine delivery rate and total contrast dose used for the two contrast agents. In the present study, the goal was to achieve more generally applicable results, independent of scan mode or scanner type used. Thus, we decided to measure the heart rate for a longer period of time and

independently of the image acquisition itself to achieve a clear result with regard to the influence of the agents on heart rate. The start of the heart rate assessment was initiated together with the start of the contrast injection, and was expanded to a period of six minutes. Thus, the differences in heart rate behavior during and after contrast injection between the two agents, as demonstrated in the present study, represents the realistic influence of the agents on the heart rate, independent of scanner and scan mode. This seems to be of special importance, since heart rate changes are becoming more of a factor with the reduced temporal resolution of current scanners. In the present study, a second-generation, state-of-the-art scanner was used, which provided high temporal resolution. However, even in this setting, image quality was compromised by the heart rate changes induced by the monomeric contrast agent. It might be that the negative influence of this contrast-material-induced heart rate rise could be more severe when using scanners with a lower temporal resolution. Another important difference of this study, when compared to previously published studies, is the fact that the same total iodine doses and iodine delivery rates were used within similar body weight groups. This leads to the conclusion that the heart rate rise is not induced by the iodine itself, but by the structure of the contrast agent used. This is further underlined by the relevant difference in subjective sensations that were reported by the patients. Despite the higher injection flow rate in the iodixanol group, heat sensation was lower and less frequent in this group.

This prospective study is not without limitations. First, different scan protocols were used in this study, including differences regarding the triggering mode, as well as the acquisition parameters (i.e., kV settings). Although the use of different scan modes and parameters led to some inhomogeneity of the data obtained, we decided to use an optimized scan protocol for every patient to avoid any disadvantage because of patients' participation in the study. The distribution of the different scan modes and the different kV settings was

homogeneous among the two groups due to the homogeneous distribution of body mass index. Thus, a relevant influence of these differences on study results can be excluded.

Another study limitation is represented by the fact that only patients with baseline heart rates below 70 were included. This limits the study conclusions. However, the use of beta-blockers for heart rate control during CT angiographies of the coronary arteries in patients with heart rates above 70 bpm is well-established and highly recommended [20]. Thus, it would not have been possible to include patients with baseline heart rates above 70 bpm and scan them without injecting beta-blockers. Since we aimed to assess the direct influence of iodinated contrast agents on heart rate changes during contrast injection, we decided to avoid any possible influence on the heart rate variability by beta-blockers, and, as a result, patients with high heart rates were not included in this trial.

Conclusion

The present study demonstrates an important influence of the specific contrast material chosen on image quality at CCTA. **The dimeric iodixanol showed a later-occurring and significantly lower heart rate increase, compared to the monomeric iomeprol. This was directly related to increased patient comfort, and to increased image quality when iodixanol was used.** In conclusion, this prospectively randomized trial has confirmed the potential of decreased heart rate variability and improved image quality at CCTA with the use of a dimeric contrast agent.

Conflict of interest

All authors stated to have no conflict of interest.

References

1. Taylor AJ, Cerqueira M, Hodgson JM, Mark D, Min J, O'Gara P, Rubin GD, American College of Cardiology Foundation Appropriate Use Criteria Task F, Society of Cardiovascular Computed T, American College of R, American Heart A, American Society of E, American Society of Nuclear C, North American Society for Cardiovascular I, Society for Cardiovascular A, Interventions, Society for Cardiovascular Magnetic R. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 Appropriate Use Criteria for Cardiac Computed Tomography. A Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. Circulation 2010;**122**(21):e525-55.

2. Liew GY, Feneley MP, Worthley SG. Appropriate indications for computed tomography coronary angiography. Med J Aust 2012;**196**(4):246-9.

3. Pugliese F, Mollet NR, Runza G, van Mieghem C, Meijboom WB, Malagutti P, Baks T, Krestin GP, deFeyter PJ, Cademartiri F. Diagnostic accuracy of non-invasive 64-slice CT coronary angiography in patients with stable angina pectoris. Eur Radiol 2006;**16**(3):575-82.

4. Hoffmann U, Ferencik M, Cury RC, Pena AJ. Coronary CT angiography. J Nucl Med 2006;**47**(5):797-806.

5. Husmann L, Leschka S, Desbiolles L, Schepis T, Gaemperli O, Seifert B, Cattin P, Frauenfelder T, Flohr TG, Marincek B, Kaufmann PA, Alkadhi H. Coronary artery motion and cardiac phases: dependency on heart rate -- implications for CT image reconstruction. Radiology 2007;**245**(2):567-76.

6. Hong C, Becker CR, Huber A, Schoepf UJ, Ohnesorge B, Knez A, Bruning R, Reiser MF. ECG-gated reconstructed multi-detector row CT coronary angiography: effect of varying trigger delay on image quality. Radiology 2001;**220**(3):712-7.

7. Schroeder S, Kopp AF, Kuettner A, Burgstahler C, Herdeg C, Heuschmid M, Baumbach A, Claussen CD, Karsch KR, Seipel L. Influence of heart rate on vessel visibility in noninvasive coronary angiography using new multislice computed tomography: experience in 94 patients. Clin Imaging 2002;**26**(2):106-11.

8. de Graaf FR, Schuijf JD, van Velzen JE, Kroft LJ, de Roos A, Sieders A, Jukema JW, Schalij MJ, van der Wall EE, Bax JJ. Evaluation of contraindications and efficacy of oral Beta blockade before computed tomographic coronary angiography. Am J Cardiol 2010;**105**(6):767-72.

9. Svensson A, Ripsweden J, Ruck A, Aspelin P, Cederlund K, Brismar BT. Heart rate variability and heat sensation during CT coronary angiography: Low-osmolar versus iso-osmolar contrast media. Acta Radiol 2010;**51**(7):722-6.

10. Justesen P, Downes M, Grynne BH, Lang H, Rasch W, Seim E. Injection-associated pain in femoral arteriography: a European multicenter study comparing safety, tolerability, and efficacy of iodixanol and iopromide. Cardiovasc Intervent Radiol 1997;**20**(4):251-6.

11. Manke C, Marcus C, Page A, Puey J, Batakis O, Fog A. Pain in femoral arteriography. A double-blind, randomized, clinical study comparing safety and efficacy of the iso-osmolar iodixanol 270 mgI/ml and the low-osmolar iomeprol 300 mgI/ml in 9 European centers. Acta Radiol 2003;**44**(6):590-6.

12. Skehan SJ, Rasmussen F, Gibney RG, Lindequist S, Moller-Nielsen S, Svaland MG, Kampenes VB, Bjartveit K, Greaney T, Carlsen SD, Masterson J. A comparison of a non-ionic dimer, iodixanol with a non-ionic monomer, iohexol in low dose intravenous urography. Br J Radiol 1998;**71**(849):910-7.

13. Sapoval MR, Beyssen BM, Girardot C, Musset MA, Legmann P, Brekke O, Gaux JC. Iodixanol in leg phlebography: a randomized, double-blind parallel group phase III trial comparing iodixanol to ioxaglate. Clin Radiol 1996;**51**(3):210-3.

14. Beitzke D, Wolf F, Edelhauser G, Plank C, Schernthaner R, Weber M, Nolz R, Lammer J, Loewe C. Computed tomography angiography of the carotid arteries at low kV settings: a prospective randomised trial assessing radiation dose and diagnostic confidence. Eur Radiol 2011;**21**(11):2434-44.

15. Austen WG, Edwards JE, Frye RL, Gensini GG, Gott VL, Griffith LS, McGoon DC, Murphy ML, Roe BB. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. Circulation 1975;**51**(4 Suppl):5-40.

16. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Eur Heart J 1996;**17**(3):354-81.

17. Rumberger JA, Brundage BH, Rader DJ, Kondos G. Electron beam computed tomographic coronary calcium scanning: a review and guidelines for use in asymptomatic persons. Mayo Clin Proc 1999;**74**(3):243-52.

18. Zimmermann E, Dewey M. Whole-heart 320-row computed tomography: reduction of radiation dose via prior coronary calcium scanning. Rofo 2011;**183**(1):54-9.

19. Alkadhi H, Stolzmann P, Desbiolles L, Baumueller S, Goetti R, Plass A, Scheffel H, Feuchtner G, Falk V, Marincek B, Leschka S. Low-dose, 128-slice, dual-source CT coronary angiography: accuracy and radiation dose of the high-pitch and the step-and-shoot mode. Heart 2010;**96**(12):933-8.

20. Mahabadi AA, Achenbach S, Burgstahler C, Dill T, Fischbach R, Knez A, Moshage W, Richartz BM, Ropers D, Schroder S, Silber S, Mohlenkamp S, Working group "Cardiac

CTotGCS. Safety, efficacy, and indications of beta-adrenergic receptor blockade to reduce heart rate prior to coronary CT angiography. Radiology 2010;**257**(3):614-23.

21. Shapiro MD, Pena AJ, Nichols JH, Worrell S, Bamberg F, Dannemann N, Abbara S, Cury RC, Brady TJ, Hoffmann U. Efficacy of pre-scan beta-blockade and impact of heart rate on image quality in patients undergoing coronary multidetector computed tomography angiography. Eur J Radiol 2008;**66**(1):37-41.

22. Chartrand-Lefebvre C, White CS, Bhalla S, Mayo-Smith WW, Prenovault J, Vydareny KH, Soto JA, Ozkan OS, Chughtai AR, Soulez G. Comparison of the effect of low- and iso-osmolar contrast agents on heart rate during chest CT angiography: results of a prospective randomized multicenter study. Radiology 2011;**258**(3):930-7.

23. Becker CR, Vanzulli A, Fink C, de Faveri D, Fedeli S, Dore R, Biondetti P, Kuettner A, Krix M, Ascenti G. Multicenter comparison of high concentration contrast agent iomeprol-400 with iso-osmolar iodixanol-320: contrast enhancement and heart rate variation in coronary dual-source computed tomographic angiography. Invest Radiol 2011;**46**(7):457-64.

24. Romano L, Grazioli L, Bonomo L, Xu JR, Chen KM, Dore R, Vanzulli A, Catalano C. Enhancement and safety of iomeprol-400 and iodixanol-320 in patients undergoing abdominal multidetector CT. Br J Radiol 2009;**82**(975):204-11.

25. Morcos SK, Dawson P, Pearson JD, Jeremy JY, Davenport AP, Yates MS, Tirone P, Cipolla P, de Haen C, Muschick P, Krause W, Refsum H, Emery CJ, Liss P, Nygren A, Haylor J, Pugh ND, Karlsson JO. The haemodynamic effects of iodinated water soluble radiographic contrast media: a review. Eur J Radiol 1998;**29**(1):31-46.

26. Weiland FL, Marti-Bonmati L, Lim L, Becker HC. Comparison of patient comfort between iodixanol and iopamidol in contrast-enhanced computed tomography of the abdomen and pelvis: a randomized trial. Acta Radiol 2013;**55**(6):715-724.

27. McCullough PA, Capasso P. Patient discomfort associated with the use of intra-arterial iodinated contrast media: a meta-analysis of comparative randomized controlled trials. BMC Med Imaging 2011;**11**:12.

Tables

Table 1: Iodine and contrast agent doses and delivery rates

Iodine and CA doses and delivery rates						
weight	iodine (for both CA)		iodixanol		iomeprol	
	flow (g/s)	dose (g)	flow (ml/s)	dose (ml)	flow (ml/s)	dose (ml)
<55 kg	1.76	28	5.5	88	4.4	70
50 - 100 kg	2	32	6.2	100	5	80
>100 kg	2.24	36	7	113	5.6	90

The same iodine delivery rate and thus the same iodine total dose were applied for all patients at same body weight groups. Consequently, flow rate and total volume differs between the two groups due to the differences in iodine content.

Table 2: Distribution of kV used during CCTA

	80 kV	100 kV	120 kV	140 kV
iodixanol	10	52	34	3
iomeprol	8	54	34	9

The distribution of kV settings used among the two groups was homogeneous without relevant differences between the two groups.

Table 3: HU, SNR, and CNR values

a) HU

HU	atrium	ventricle	valsalvae	LCA
iodixanol	357.5	377.6	441.4	424.7
iomeprol	342.8	359.6	424.2	404.1
p	> 0.05			

b) CNR

CNR	atrium	ventricle	valsalvae	LCA
iodixanol	17.3	18.4	21.9	21.0
iomeprol	16.7	17.6	21.2	20.3
p	> 0.05			

c) SNR

SNR	atrium	ventricle	valsalvae	LCA
iodixanol	19.2	20.3	23.7	22.8
iomeprol	18.6	19.5	23.0	21.9
p	> 0.05			

Mean values of HU, CNR, and SNR for the four predefined anatomical regions separately. No significant differences were found between iodixanol and iomeprol.

Table 4: Distribution of all scores for analyzed segments

	0	1	2	3	4	non-existent
iodixanol	0 (0.0%)	4 (0.3%)	61 (4.4%)	299 (21.5%)	1024 (73.8%)	112
iomeprol	13 (0.9%)	21 (1.4%)	92 (6.3%)	415 (28.6%)	911 (62.7%)	123

Distribution of quality assessment among all analyzed coronary segments over rating units (in absolute values and percentage of the group), as well as the number of non-existent segments due to anatomical variations (see also fig. 2).

Table 5: Average rating of segment groups (RCA, LAD, CX)

	RCA	LAD	CX
iodixanol	3.5	3.8	3.7
iomeprol	3.3	3.6	3.5
p	< 0.001	< 0.001	< 0.001

The average of quality ratings among different vascular territories showed a significant difference between the two groups.

Equations

Equation 1

$$CNR = \frac{HUves - HUmusc}{SDBN}$$

Equation 2

$$SNR = \frac{HUves}{SDBN}$$

Equation 3

$$SDNN = \sqrt{\frac{1}{N-1}\sum_{i-2}^{N}(RR_i - \overline{RR})^2}$$

Equation 4

$$RMSSD = \sqrt{\frac{1}{N-2}\sum_{i-3}^{N}(RR_i - RR_{i-1})^2}$$

Figures

Figure 1:

This figure exemplifies the evel of ROI measurements for assessment of contrast enhancement. A circular ROI with an area of about 1 cm^2 was placed in the left atrium and left ventricle, a ROI with an area of about 0.4 cm^2 was placed in the sinus valsalvae, and about 0.05 cm^2 in the LCA.

Figure 2:

This figure exemplifies on the RCA the quality rating for every coronary segment. Image quality was described on a scale from zero to four (0: not assessable; 1: poor quality, more than 50% of segments not assessable; 2: suboptimal quality, diagnosis hampered; 3: good quality, diagnosis possible without limitations; 4: excellent quality, no limitations).

Figure 3:

Course of heart rate deviation from baseline during the first 60 seconds after contrast injection for the entire study population (including all body weight groups)

Figure 4:

Course of heart rate deviation from baseline during the first 60 seconds after contrast injection for the mid body weight group (55 – 100 kg) (n = 175).

Figure 5:

Boxplot of the heat-sensations during the contrast administration as indicated by the patients using a visual score.