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Impact of iodine concentration and iodine delivery rate on contrast enhancement in coronary CT angiography: a randomized multicenter trial (CT-CON)

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Abstract

Objective To compare the effect of contrast medium iodine concentration on contrast enhancement, heart rate, and injection pressure when injected at a constant iodine delivery rate in coronary CT angiography (CTA).

Methods One thousand twenty-four patients scheduled for coronary CTA were prospectively randomized to receive one of four contrast media: iopromide 300 mg I/ml, iohexol 350 mg I/ml, iopromide 370 mg I/ml, or iomeprol 400 mg I/ml. Contrast media were delivered at an equivalent iodine delivery rate of 2.0 g I/s. Intracoronary attenuation was measured and compared (per vessel and per segment). Heart rate before and after contrast media injection was documented. Injection pressure was recorded ($n = 403$) during contrast medium injection and compared between groups.

Results Intracoronary attenuation values were similar for the different contrast groups. The mean attenuation over all segments ranged between 384 HU for 350 mg I/ml and 395 HU for 400 mg I/ml ($p = 0.079$). Dose-length product ($p = 0.8424$), signal-to-noise ratio (all $p > 0.05$), time to peak ($p = 0.324$), and changes in heart rate ($p = 0.974$) were comparable between groups. The peak pressures differed: 197.4 psi for 300 mg I/ml (viscosity 4.6 mPa s), 229.8 psi for 350 mg I/ml (10.4 mPa s), 216.1 psi for 370 mg I/ml (9.5 mPa s), and 243.7 psi for 400 mg I/ml (12.6 mPa s) ($p < 0.0001$).

Conclusion Intravascular attenuation and changes in heart rate are independent of iodine concentration when contrast media are injected at the same iodine delivery rate. Differences in injection pressures are associated with the viscosity of the contrast media.

Key Points

- *The contrast enhancement in coronary CT angiography is independent of the iodine concentration when contrast media are injected at body temperature (37 °C) with the same iodine delivery rate.*
- *Iodine concentration does not influence the change in heart rate when contrast media are injected at identical iodine delivery rates.*
- *For a fixed iodine delivery rate and contrast temperature, the viscosity of the contrast medium affects the injection pressure.*

Keywords Contrast media · Computed tomography angiography · Coronary disease · Randomized controlled trial

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Abbreviations

AE	Adverse events
AHA	American Heart Association
ANOVA	Analysis of variance
BPM	Beats per minute
CTA	Computed tomography angiography
CX	Circumflex artery
DLP	Dose-length product
ECG	Electrocardiogram
HU	Hounsfield units
IDR	Iodine delivery rate
IQR	Interquartile range
LAD	Left anterior descending artery
LMCA	Left main coronary artery
MDRD	Modification of Diet in Renal Disease
RCA	Right coronary artery
ROI	Region of interest
SD	Standard deviation
SNR	Signal-to-noise ratio

Introduction

Non-invasive coronary computed tomography angiography (CTA) has become an established tool for the diagnosis of coronary artery disease [1]. Image quality and overall diagnostic accuracy rely on sufficiently high intravascular attenuation [2], which is especially important for the evaluation of the smaller—but clinically relevant—distal coronary segments [3]. The attenuation of vascular structures is determined by various factors, including the intravascular iodine concentration, which depends on the contrast medium injection protocol, but also on patient size and circulation time [4].

Injection-related parameters influencing the contrast enhancement include the concentration and volume of the contrast medium as well as the injection rate [5]. The combination of the iodine concentration of the contrast medium and the injection rate can be represented as the iodine delivery rate (IDR). To date, it is unclear which injection parameter is most important for adequate contrast enhancement [5]. Rather than solely one parameter, it is thought that a combination of parameters (e.g., IDR) will be the most decisive factor for intravascular attenuation in coronary CTA protocols [5].

Extensive research has been conducted on the influence of contrast medium iodine concentration on intravascular enhancement. Yet, current evidence is controversial as to whether a more highly concentrated contrast medium is beneficial in terms of contrast enhancement, particularly when the IDR is kept identical [5]. High-iodine contrast media have the potential to increase the contrast enhancement, as the degree of intravascular attenuation depends on the amount of iodine within the vessels [6]. However, higher iodine concentrations are directly related to a higher viscosity of the contrast medium. A high viscosity leads to elevation of the injection pressure and, depending on the injection protocol, can result in a weaker-than-expected contrast enhancement [6].

We hypothesize that the contrast enhancement in coronary CTA is independent of the iodine concentration when the IDR is identical. Hence, the primary objective of this study is to explore the impact of iodine concentration on intracoronary attenuation at a fixed IDR. In addition, we describe the effect of the iodine concentration on the time to peak and on pressure curves during contrast medium injection.

Materials and methods

Study design

The CT-CON trial (CT coronary angiography: effect of iodine CONcentration on vascular attenuation) is a randomized, controlled trial, performed at six centers in the Netherlands and Italy. Coronary enhancement and injection characteristics of four commonly used contrast media for coronary CTA were compared. Approval of the study was obtained by the local ethics review committee at each of the centers, and all patients gave informed consent in writing.

Study population

Patients at least 18 years of age and scheduled for coronary CTA to rule out coronary artery disease were included in the study. Exclusion criteria included renal insufficiency (estimated creatinine clearance below 50 ml/min using the MDRD equation [MDRD = Modification of Diet in Renal Disease]), a history of hypersensitivity to iodinated contrast media, persistent cardiac arrhythmias, the inability to breath hold for 10 s, possible pregnancy, a body weight greater than 120 kg, and inability to give informed consent. No patients with stents or grafts were included.

Patients were prospectively randomized into four groups. In each group, a different contrast medium was administered: group IP300 received iopromide 300 mg I/ml (Ultravist®, Bayer Healthcare), group IH350 received iohexol 350 mg I/ml (Omnipaque®, GE Healthcare), group IP370 received iopromide 370 mg I/ml (Ultravist®, Bayer), and group IM400 received iomeprol 400 mg I/ml (Iomeron®, Bracco).

Contrast medium injection protocol

All contrast media were warmed to 37 °C before the injection and injected with an IDR of 2.0 g I/s. The associated maximum flow rate during the injection was recorded for each patient. The maximum pressure threshold was set to 325 psi for all injections. A standard tubing system with a fixed length was used in all patients, and contrast media were injected into an antecubital vein using an 18-gauge intravenous catheter.

To achieve an iodine delivery rate of 2 g I/s, the injection rate was calculated as

$$\text{injection flow rate (ml/s)} = \text{iodine delivery rate (2000 mg/s)}/\text{iodine concentration (mg/ml)}$$

The injection duration was derived according to the following formula:

$$\text{injection duration (s)} = \text{scan time (s)} + 6\text{ s (delay from trigger)}$$

The injection duration was then used to calculate the contrast medium volume:

$$\text{contrast medium volume (ml)} = \text{injection duration (s) x injection flow rate (ml/s)}$$

A constant iodine delivery rate was used, independent of body size. A fixed volume of 40 ml of saline was administered after the contrast medium bolus at the same flow rate.

Coronary CTA protocol

All scans were acquired on single- or dual-source scanners with at least 32 detector rows. Three centers used a 32 × 2-row dual-source scanner (Somatom Definition, Siemens Healthcare), two centers a 128-row single-source scanner (Somatom Definition AS, Siemens Healthcare), and one center a 64-row single-source scanner (Lightspeed VCT, GE Medical Systems). All centers were equipped with the same contrast medium dual-head injector (Medrad® Stellant, Bayer). At two centers, injection parameters including injection flow rate and contrast medium volume were recorded (Certegra® P3T, Bayer).

Premedication with intravenous beta-blockers (metoprolol or atenolol) was administered in all patients with a heart rate greater than 65 bpm. Sublingual nitroglycerin (0.8 mg) was given to all patients immediately before the contrast-enhanced acquisition.

The non-enhanced coronary calcium scan was performed in prospectively electrocardiogram (ECG)-triggered axial scan mode. A bolus-tracking technique was used to synchronize the image acquisition with the contrast medium arrival by placing a region of interest (ROI) in the ascending aorta; the threshold for the start of the scan was set at 100 HU. Images were acquired every 1.0–1.25 s with a tube voltage of 120 kV and a current of 40 mAs. Coronary CTA acquisition started 6 s after reaching the threshold in the ascending aorta. All acquisitions were performed in cranio-caudal direction from the ascending aorta (exactly at the level of the monitoring acquisition) to the cardiac apex. Depending on the patient's heart rate, the CT scan was conducted either in spiral scan mode with ECG-gated image reconstruction or in prospectively ECG-triggered axial scan mode. For the spiral scan mode, prospectively ECG-triggered tube modulation was used with an 80% nominal dose reduction outside the cardiac phase of interest. Tube power was modulated depending on the patient's body size using a z-axis tube current modulation (700 mAs for single-source and 350 mAs/tube for dual-source scanners). Images were reconstructed with a slice thickness of 0.75 mm, an increment of 0.4 mm, and a smooth cardiac kernel. Dose-length product (DLP; in mGy × cm) was recorded for all acquisitions.

Pressure curves, time to peak, and the peak pressure value (maximum contrast injection pressure measured in pound-force per square inch [psi]) were recorded at 2 sites for a total of 403 patients (98 patients in group IP300, 101 in group IH350, 102 in group IP370, and 102 in group IM400).

Image analysis

Prior to analysis, the patient data were anonymized by an independent radiologist not involved in imaging analysis.

Quantitative analysis

Quantitative analysis was performed by two expert radiologists in consensus, who were blinded to the contrast medium injection protocol used. Analyses were performed using dedicated CT post-processing software (Circulation®, Siemens). Before the analysis, both readers determined whether the image data sets were technically adequate for quantitative assessment. If major artifacts were present, no further analysis was performed.

Attenuation values were measured within a circular ROI of approximately 2 mm^2 in the lumen of the left main artery and proximal, middle, and distal segments of the left anterior descending artery (LAD), right coronary artery (RCA), and circumflex artery (CX). Attenuation values in the right ventricle, left ventricle, right atrium, left atrium, and ascending and descending aortae were recorded with a ROI of approximately 1 cm^2. The segmental anatomy of the coronary arteries was defined according to the American Heart Association (AHA) classification [7]. The signal-to-noise ratio (SNR) was calculated for each measurement by dividing the attenuation values in the coronary lumen by the standard deviation measured in the left ventricular cavity.

Qualitative analysis

An independent radiologist, blinded to patient clinical information and contrast medium injection protocol, reviewed all CT datasets and evaluated image quality using a four-point score (0 = low; 1 = poor; 2 = good; 3 = excellent), taking into account the degree of enhancement and the presence of beam hardening or movement artifacts.

Heart rate measurement

The CT system records an ECG tracing during data acquisition. From these tracings, the heart rate of each patient was recorded during the non-enhanced coronary calcium scan and the CTA (both during breath hold).

Statistical analysis

First, a calculation of the optimal sample size was performed. Previous studies have demonstrated an intracoronary attenuation of 390 HU, with a standard deviation of nearly 80 HU [8–10]. A difference of 30 HU is considered clinically relevant. To reach a power of 0.90 and a two-tailed α of 0.05 with Bonferroni correction for 6 intergroup comparisons, at least 221 subjects need to be included in each of the 4 groups, with a total of 884 patients.

Descriptive and univariate statistics were performed on demographic data to assess the homogeneity of the four groups. Differences between groups were analyzed using a χ^2 test with Yates correction for the patients' sex distribution and using a Student's t test for patients' height, weight, age, and body mass index.

Intracoronary attenuation, peak pressure, time-to-peak values, and heart rate variation were compared by means of a univariate analysis of variance (ANOVA) followed by Bonferroni's multiple comparison test or by Kruskal-Wallis test with Dunn's multiple comparison. The quantitative analysis was performed on a per-vessel (left main coronary artery [LMCA] and LAD, CX, and RCA) and per-segment (proximal, middle, and distal) basis.

Qualitative scores and SNR were analyzed using an independent-samples t test. For the comparison of pressure curves, the area under the curve for each time point was calculated and these were then compared between all groups with the Kruskal-Wallis test followed by a Dunn's multiple comparison test.

For all statistical analyses, a p value of less than 0.05 was considered to indicate statistically significant differences. Values are presented as means ± standard deviation (SD) unless specified otherwise.

Safety

All early adverse events (AEs) to contrast media injection such as allergic reactions or extravasation were recorded. Safety monitoring was performed up to 1 h after the end of the examination.

Results

A total of 1055 patients were enrolled in the study. Thirty-one patients were excluded due to missing documentation or deviation from the protocol, or because CTA was not performed (Fig. 1). In total, 1024 patients were randomly assigned to four contrast media: 254 patients to IP300, 251 to IH350, 258 to IP370, and 261 to IM400. Calcium score, body mass index, age, and gender distribution were similar among the groups (Table 1).

Scan performance

As per protocol, the total contrast medium volume was proportionally higher for the groups with lower iodine concentration. Injected volumes increased with decreasing iodine concentration (Table 2): 119.7 ± 21.1 ml of contrast medium was injected in group IP300 compared to 89.6 ± 14.4 ml in group IM400. However, the total iodine dose was similar between the groups ($p = 0.953$) (Table 2). Injection rates were 6.7 ml/s in group IP300, 5.7 ml/s in group IH350, 5.4 ml/s in group IP370, and 5.0 ml/s in group IM400. The DLP was similar between groups (Table 2). No contrast medium extravasations were observed.

Time-to-peak values were comparable between the groups ($p = 0.324$) and ranged from 17.9 ± 2.9 s in group IH350 to 18.9 ± 3.6 s in group IM400 (Table 2). However, there were differences between the measured peak pressures (Fig. 2): 197.4 ± 47.6 psi in group IP300, 229.8 ± 35.6 psi in group IH350, 216.1 ± 46.1 psi in group IP370, and 243.7 ± 58.6 psi in group IM400 (Table 2). The maximum pressure of 325 psi was reached in none of the exams. Pairwise analysis of the peak pressure revealed a lower mean value in group IP300 than in the other groups ($p < 0.05$). A lower peak pressure was also observed in group IP370 compared to IM400 ($p < 0.05$). No differences in peak pressure were observed for the comparison of IH350 with IP370 and IM400. Statistical differences were found for the comparison of the pressure curves of IP300 with IH350 and IM400 ($p < 0.05$) (Fig. 3).

The mean heart rate during the non-enhanced coronary calcium scan and during the coronary CTA was similar between groups (Table 2). The heart rate difference ranged from 1.4 to 1.8 bpm, with no significant differences between groups. Retrospective and prospective gating, which were chosen depending on the patient's heart rate, were used in equal rates (Table 2).

Coronary enhancement and image quality

A total of 3060 vessels (1024 LAD, 1018 CX, and 1018 RCA) and 9443 segments were analyzed (4077 proximal, 2907 middle, and 2459 distal). Similar attenuation values among groups were observed in the per-patient analysis performed on all

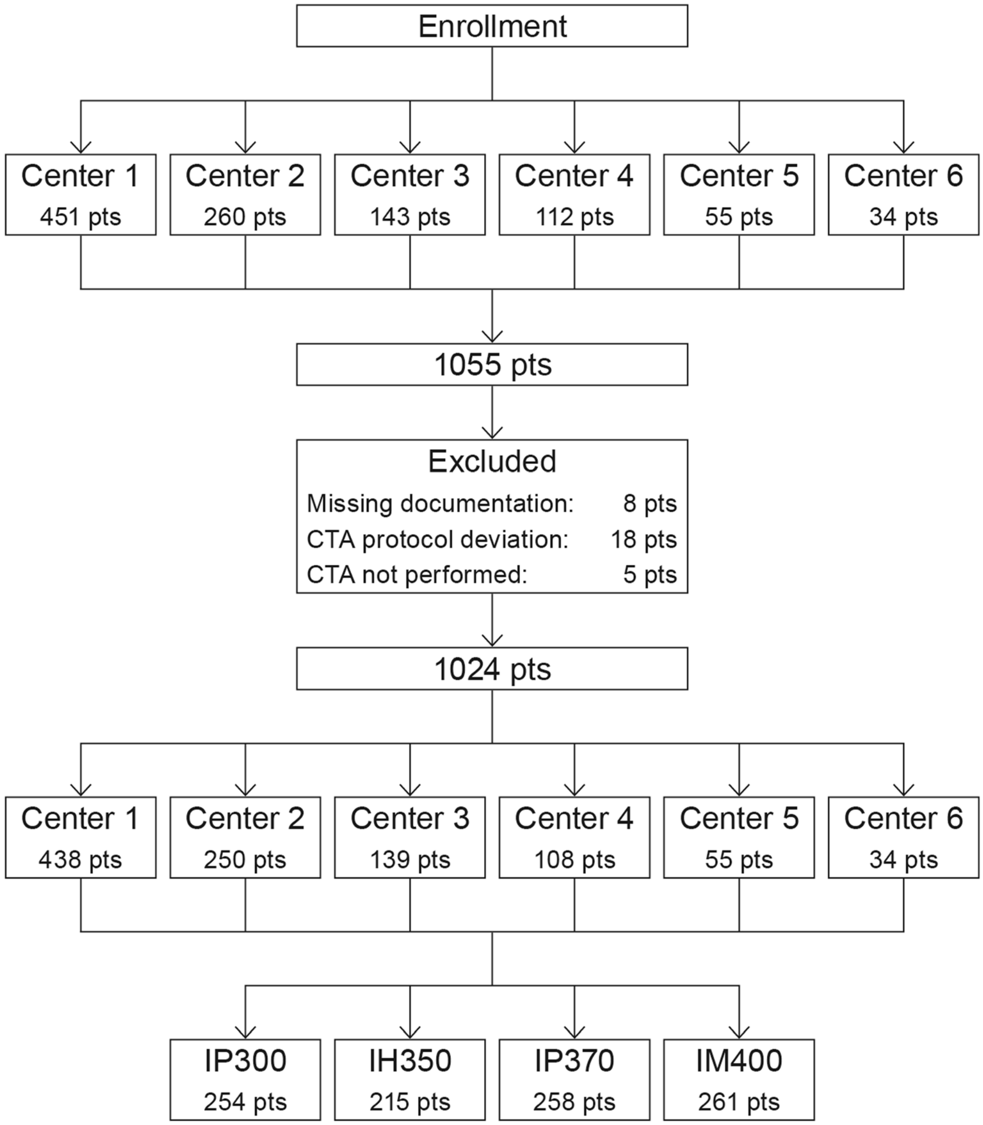

Fig. 1 Flow chart illustrating enrollment, exclusion, and randomization of patients to iopromide 300 mg I/ml (IP300), iohexol 350 mg I/ml (IH350), iopromide 370 mg I/ml (IP370), or iomeprol 400 mg I/ml (IM400)

coronary segments, varying from 384 ± 54 HU for IH350 to 395 ± 63 HU for IM400, and in the per-vessel and per-segment analysis (Table 3). Stratified by scan mode, measured attenuation values for all coronary segments were similar within each contrast group: IP300 390 ± 72 HU versus 378 ± 70 ($p = 0.23$); IH350 370 ± 62 HU versus 379 ± 69 ($p = 0.42$); IP370 386 ± 57 HU versus 376 ± 75 ($p = 0.13$); IM400 385 ± 70 HU versus 380 ± 73 ($p = 0.77$), for the prospective ECG-triggered axial scan mode and retrospective ECG-gated spiral scan mode respectively. No significant differences were observed between the groups in terms of attenuation of the ascending and descending aortae, right and left atria, or right and left ventricles. The mean rating for the image quality was above 2.8 on a scale from 0 (low) to 3 (excellent) for all analyses, indicating mostly excellent image quality (Table 4). No significant differences in terms of SNR were observed between the groups (Table 4).

Discussion

The CT-CON study is the largest randomized comparison of contrast media for coronary CTA to date. We compared contrast enhancement of contrast media with various iodine concentrations injected at the same IDR. No statistically significant differences were observed for the intracoronary attenuation. This finding demonstrates that injection of contrast media with different iodine concentrations at identical IDRs results in similar contrast enhancement in coronary CTA. Further, SNR and time to peak were comparable, as were the heart rate changes from non-enhanced coronary calcium scan to coronary CTA. Clear differences between the contrast media were observed for the pressure curves and the peak pressure.

Attempts to compare the effect of different contrast media on the contrast enhancement in coronary CTA have been

Table 1 Patient characteristics

	IP300	IH350	IP370	IM400	*p* value
Patients	254	251	258	261	
Age (years)	54.7 ± 10.2	53.6 ± 10.1	55.0 ± 9.3	55.9 ± 9.6	0.111**
Female sex	44 (17.3)	41 (16.3)	40 (15.5)	40 (15.3)	0.633*
Body mass index (kg/m^2)	26.8 ± 3.9	26.7 ± 4.6	26.7 ± 3.7	27.0 ± 4.2	0.906**
Agatston calcium score, median (IQR)	3.0 (75.8)	3.3 (95.6)	6.5 (106.9)	3.0 (109.8)	0.839**
Cardiovascular risk factors					
Current/past smoker	53 (20.9)	58 (23.1)	60 (23.3)	52 (19.9)	0.871*
Hypertension[a]	94 (37.0)	94 (37.4)	97 (37.6)	87 (33.3)	0.887*
Dyslipidaemia[b]	86 (33.9)	90 (35.8)	102 (39.5)	90 (34.5)	0.866*
Diabetes mellitus[c]	20 (7.9)	39 (15.5)	35 (13.6)	20 (7.7)	0.274*
Family history of ischemic heart disease	98 (38.6)	101 (40.2)	119 (46.1)	112 (42.9)	0.745*
Symptoms					
Typical chest pain	44 (17.3)	58 (23.1)	43 (16.7)	40 (15.3)	0.486*
Atypical chest pain	24 (9.4)	32 (12.7)	28 (10.9)	38 (14.6)	0.594
No chest pain	186 (73.2)	161 (64.1)	187 (72.5)	183 (70.1)	0.511*
Previous myocardial infarction	17 (6.7)	15 (6.0)	16 (6.2)	15 (5.7)	0.988*

No significant differences were observed between groups. All values are mean ± standard deviation or *N* (%) unless otherwise specified

IQR interquartile range

[a] Hypertension: > 150 mmHg systolic or > 90 mmHg diastolic or using tension-lowering medication

[b] Dyslipidemia: total cholesterol > 5 mmol/l, low-density lipoprotein > 3 mmol/l, or on lipid-lowering medication

[c] Diabetes mellitus: plasma glucose > 11.0 mmol/l, or treated with diet regulation or medication

*Chi-square test

**One-way ANOVA

complicated by large variations regarding scan technique, patient characteristics, and contrast medium injection protocols [5]. There are reports in the literature that the contrast enhancement depends on the iodine concentration [9, 10, 14], but other studies have shown that the contrast enhancement is independent of the iodine concentration [2, 4, 15–17]. Our findings are in line with results from studies conducted in circulating phantoms [4, 15] and in patients [2, 16, 17] that did not find any dependency of the intravascular attenuation on iodine concentration at identical IDR. In circulating phantoms, attenuation was independent of iodine concentration for contrast media with 240 to 400 mg I/ml injected at an IDR of 2.0 g I/s [15] and for contrast media with 300 to 400 mg I/ml injected at an IDR of 1.8 g I/s [4]. Studies investigating the contrast enhancement in patients using contrast media with iodine concentrations of 240 and 300 mg I/ml ($N = 100$) [2]; 240, 300, and 370 mg I/ml ($N = 200$) [16]; and 270 and 300 mg I/ml ($N = 306$) [17] injected at a comparable IDR also found no dependency of intravascular attenuation on iodine concentration. The use of injection protocols with constant flow rates, rather than a fixed IDR, may explain the observation of increased attenuation values with higher iodine concentrations: at identical flow rates, the amount of iodine delivered per unit of time is higher for high-iodine contrast media and, hence, the attenuation is increased compared to a low-iodine contrast medium.

Current evidence suggests that image quality is independent of contrast medium iodine concentration [2, 4]. Here, the image quality was rated excellent for most comparisons, with mean values of either 2.8 or 2.9 on a scale from 0 to 3. Yet, we found significant differences between contrast medium groups. That the small differences in image quality were statistically significant suggests that the study was overpowered for the analysis of image quality. The large number of patients included in this study was based on optimal sample size calculation for contrast enhancement and not for image quality. Although statistically significant, the small differences in image quality are unlikely to be of clinical relevance.

The occurrence of cardiac imaging artifacts can be reduced by lowering the heart rate and minimizing heart rate variability [18]. Low-osmolar contrast media may influence the heart rate. An increase of 5 bpm was observed after iopamidol 370 injection at a fixed flow rate [19], while the heart rate remained basically unchanged (+ 0.32 bpm) upon injection of iopromide 300 at a fixed IDR [17]. Svensson et al reported more rhythm variation and heat sensations with low-osmolar iomeprol (400 mg I/ml) than with iso-osmolar iodixanol (320 mg I/ml) [20], although other studies found no

Table 2 Scan characteristics

	IP300	IH350	IP370	IM400	*p* value
Scanning technique					
Spiral scan mode	138 (54.3)	121 (48.2)	128 (49.6)	133 (51.0)	
Axial scan mode	116 (45.7)	130 (51.8)	130 (50.4)	128 (49.0)	
Tube current range (mAs)	230–410	219–410	256–410	214–410	
Tube voltage (kV)	120	120	120	120	
Contrast injection					
Contrast medium	Iopromide	Iohexol	Iopromide	Iomeron	
Iodine concentration (mg I/ml)	300	350	370	400	
Injection rate (ml/s)	6.7	5.7	5.4	5.0	
CM volume (ml)	119.7 ± 21.2	103.0 ± 17.4	96.6 ± 15.2	90.0 ± 14.5	0.0001
Total iodine dose (g)	35.9 ± 6.4	36.1 ± 6.1	35.7 ± 5.6	35.8 ± 5.8	0.953
Time to peak (s)	18.1 ± 3.8	17.9 ± 2.9	18.7 ± 3.9	19.0 ± 3.6	0.324
Peak pressure (psi)	197.4 ± 47.7	229.8 ± 35.7	216.1 ± 46.1	243.7 ± 58.7	0.0001
Heart rate					
During calcium scan (bpm)[a]	62.5 ± 9.3	63.1 ± 9.4	64.1 ± 11.4	62.3 ± 10.2	0.115
During CTA (bpm)	64.3 ± 10.7	64.6 ± 10.8	65.5 ± 12.6	63.9 ± 11.7	0.431
Difference (bpm)	1.8 ± 6.7	1.6 ± 6.1	1.4 ± 6.5	1.6 ± 5.8	0.974
Radiation dose					
Overall DLP (mGy/cm)	608.6 ± 394.3	592.3 ± 366.3	599.2 ± 383.9	628.1 ± 431.3	0.8424
For spiral scan mode	807.6 ± 468.4	845.4 ± 424.7	900.9 ± 444.2	879.6 ± 530.6	0.7822
For axial scan mode	429.6 ± 176.3	418.6 ± 170.1	429.2 ± 234.5	435.5 ± 168.4	0.3694

All values are mean ± standard deviation or *N* (%) unless otherwise specified

bpm beats per minute, *CM* contrast medium, *DLP* dose-length product

[a] The heart rate during the coronary calcium scan was determined as the mean over 15 s

differences in heart rate or variability between low- and iso-osmolar contrast media [19]. In this study, we observed slightly higher heart rates (1.4–1.8 bpm) during the CTA than during the coronary calcium scan, with similar changes in heart rate between contrast groups. These results indicate that injection of low-osmolar contrast media at a fixed IDR has only slight effects on the heart rate, independent of iodine concentration.

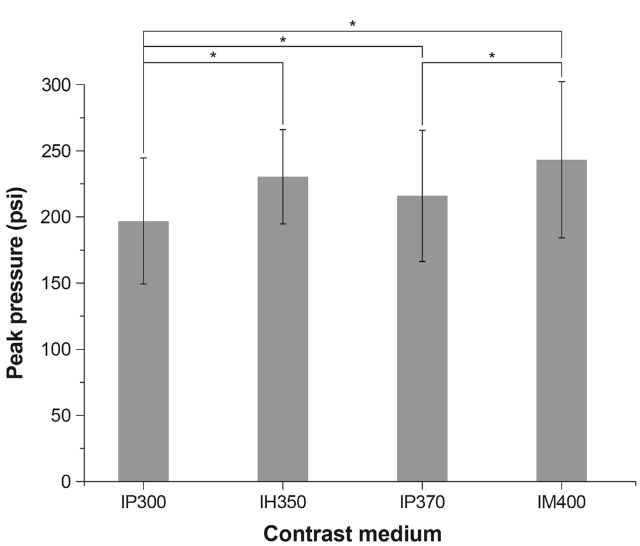

Fig. 2 Comparison of peak pressure values for the contrast media 300 mg I/ml (IP300), iohexol 350 mg I/ml (IH350), iopromide 370 mg I/ml (IP370), and iomeprol 400 mg I/ml (IM400). $*p < 0.05$

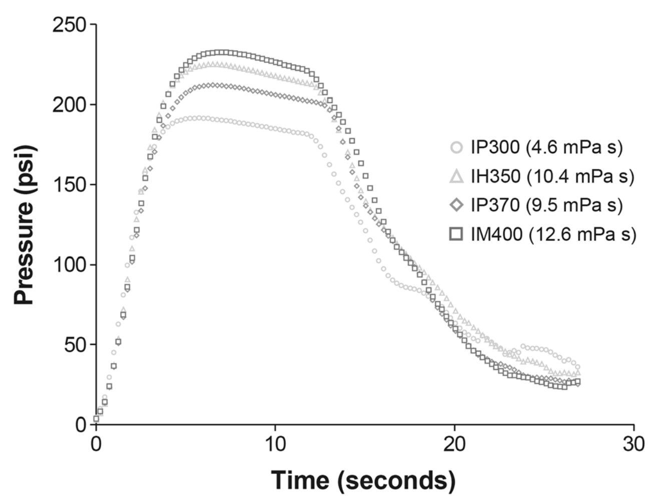

Fig. 3 Pressure-time curves for the injection of iopromide 300 mg I/ml (IP300), iohexol 350 mg I/ml (IH350), iopromide 370 mg I/ml (IP370), and iomeprol 400 mg I/ml (IM400) at a fixed IDR of 2 g I/s. The viscosity values at 37 °C (in mPa s) from the respective prescribing information are also given [11–13]

Table 3 Attenuation values (HU) measured in coronary arteries, aortae, and cardiac chambers

	IP300	IH350	IP370	IM400	*p* value
Coronary arteries					
All segments	391 ± 42	384 ± 55	394 ± 55	396 ± 63	0.079
Left anterior descending	392 ± 73	383 ± 53	395 ± 45	394 ± 42	0.068
Left circumflex branch	382 ± 71	365 ± 106	371 ± 89	367 ± 80	0.132
Right coronary artery	403 ± 115	396 ± 99	420 ± 116	414 ± 111	0.069
Proximal segments	415 ± 42	407 ± 49	416 ± 44	415 ± 47	0.074
Middle segments	390 ± 71	387 ± 93	401 ± 72	398 ± 73	0.169
Distal segments	352 ± 70	351 ± 72	352 ± 103	348 ± 100	0.944
Aorta					
Ascending aorta	434 ± 89	428 ± 71	444 ± 81	455 ± 211	0.088
Descending aorta	418 ± 88	404 ± 73	418 ± 83	423 ± 81	0.060
Cardiac chambers					
Left atrium	385 ± 100	393 ± 92	394 ± 98	389 ± 104	0.709
Right atrium	159 ± 75	155 ± 90	155 ± 84	151 ± 78	0.789
Left ventricle	403 ± 244	406 ± 209	398 ± 92	390 ± 96	0.755
Right ventricle	181 ± 81	174 ± 92	173 ± 91	170 ± 81	0.522

All values are expressed as Hounsfield units (HU) with mean and standard deviation. Segments are classified according to the American Heart Association (AHA); for more details, see "Materials and methods"

The viscosity of the contrast medium can affect delivery and the frequency of adverse events related to intravenous administration [21, 22]. In general, low-osmolar contrast media have a lower viscosity than iso-osmolar contrast media, and for low-osmolar contrast media, the viscosity increases exponentially with increasing iodine concentration (Fig. 4) [23]. In this study, we observed the highest peak pressure for IM400 and the lowest for IP300, as would be expected. Interestingly, the peak pressure was numerically higher for IH350 than for IP370 and the pressure curve also showed a clear trend to higher pressure values for IH350, although the differences were not statistically significant. A closer look at the viscosities of IH350 and IP370 reveals that despite having a lower iodine concentration the viscosity of IH350 at 37 °C is higher than that of IP370 (10.4 mPa s vs. 9.5 mPa s) (Fig. 4). As a lower viscosity is known to be beneficial in terms of

Table 4 SNR and image quality in coronary arteries, aortae, and cardiac chambers

	IP300	IH350	IP370	IM400	*p* value
Signal-to-noise ratio					
All segments	20 ± 12	20 ± 11	23 ± 21	22 ± 16	0.711
Left anterior descending	21 ± 13	20 ± 10	22 ± 19	22 ± 16	0.906
Left circumflex branch	18 ± 13	17 ± 14	20 ± 24	18 ± 16	0.332
Right coronary artery	21 ± 12	20 ± 11	22 ± 19	23 ± 17	0.771
Proximal segments	21 ± 13	20 ± 12	24 ± 23	23 ± 18	0.928
Middle segments	20 ± 12	18 ± 11	20 ± 18	20 ± 15	0.240
Distal segments	18 ± 11	17 ± 10	19 ± 17	20 ± 15	0.713
Image quality					
All segments	2.9 ± 0.4	2.9 ± 0.3	2.8 ± 0.2	2.9 ± 0.2	< 0.0001
Left anterior descending	2.9 ± 0.3	2.9 ± 0.3	2.9 ± 0.2	2.9 ± 0.2	0.032
Left circumflex branch	2.9 ± 0.4	2.9 ± 0.3	2.9 ± 0.3	2.9 ± 0.3	0.007
Right coronary artery	2.8 ± 0.5	2.8 ± 0.4	2.8 ± 0.4	2.8 ± 0.3	0.228
Proximal segments	2.9 ± 0.3	2.9 ± 0.3	2.9 ± 0.2	2.9 ± 0.2	0.089
Middle segments	2.8 ± 0.4	2.8 ± 0.3	2.8 ± 0.3	2.9 ± 0.3	0.042
Distal segments	2.8 ± 0.5	2.8 ± 0.4	2.8 ± 0.3	2.8 ± 0.3	0.006

All values are expressed as mean and standard deviation. Segments are classified according to the American Heart Association (AHA); for more details see "Materials and methods"

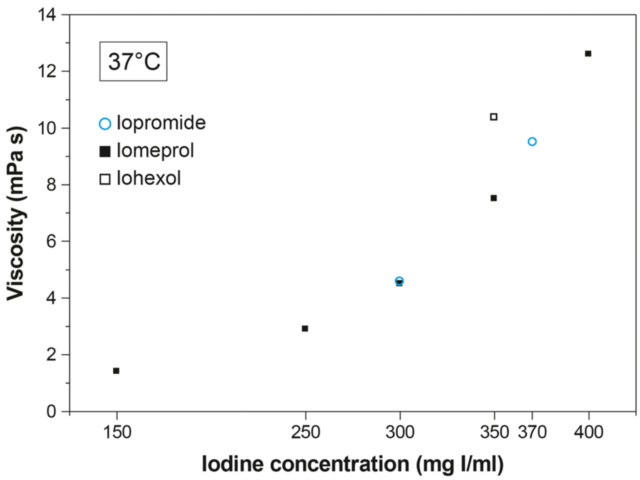

Fig. 4 Exponential increase of iomeprol viscosity with increasing iodine concentration. The values for iopromide 300 mg I/ml, iohexol 350 mg I/ml, and iopromide 370 mg I/ml are also shown. All viscosity values are for 37 °C as stated in the respective prescribing information [11–13]

injection pressure [6, 24], the observed higher peak pressure and pressure curve for IH350 than for IP370 are most likely a viscosity-related effect.

Possible confounding factors in this study include potentially different contrast kinetics for the contrast injection protocols, which could result in different captures of the enhancement plateau. We used a fixed tube voltage of 120 kV, which was the clinical standard at the time. Contemporary CT systems allow for lower tube voltages in smaller patients, necessitating smaller contrast volumes to achieve similar contrast enhancement. More efficient use of contrast medium without sacrificing vessel enhancement can be accomplished by individually optimized contrast enhancement protocols as recently demonstrated by Matsumoto et al [25] Although inter- and intraobserver variability was not assessed, this should not affect the study results because of the randomized study design and blinded reading of the images. We did not investigate the diagnostic accuracy for the detection of coronary stenoses because invasive angiography was not clinically needed in the vast majority of patients.

Conclusions

When injected at the same iodine delivery rate, contrast media with different iodine concentrations provide similar contrast enhancement and changes in heart rate are comparable.

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Compliance with ethical standards

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Statistics and biometry One of the authors has significant statistical expertise.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional Review Board approval was obtained.

Methodology
• prospective.
• randomized controlled trial.
• multicenter study.

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