# 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*

*Cristoph R. Becker, MD,* Angelo Vanzulli, MD,† Christian Fink, MD,‡ Daniele de Faveri, MD,§ Stefano Fedeli, MD,¶ Roberto Dore, MD,‖ Pietro Biondetti, MD,** Alex Kuettner, MD,†† Martin Krix, MD,‡‡ and Giorgio Ascenti, MD§§*

**Objectives:** To compare a contrast agent with high iodine concentration with an iso-osmolar contrast agent for coronary dual-source computed tomography angiography (DS-CTA), and to assess whether the contrast agent characteristics may affect the diagnostic quality of coronary DS-CTA.

**Materials and Methods:** Patients were randomized to receive either 80 mL of iodixanol-320 (Visipaque, GE Healthcare, Chalfont St. Giles, United Kingdom) or iomeprol-400 (Iomeron, Bracco Imaging SpA, Milan, Italy) at 5 mL/s. Mean, minimum, maximum heart rate, and its variation (max-min) were assessed during calcium scoring scan and coronary DS-CTA. Three off-site readers independently evaluated the image sets in terms of technical adequacy, reasons for inadequacy, vessel visualization, diagnostic confidence (based on a 5-point scale), and arterial contrast opacification in Hounsfield units (HUs).

**Results:** Ninety-six patients were included in the final evaluation. No significant differences were observed for pre- and postdose heart rate values for iomeron-400 compared with iodixanol-320, and changes in heart rate variation were also not significantly different ($-2.3 \pm 11.7$ vs. $-2.5 \pm 7.3$ bpm, $P > 0.1$). Contrast measurements in all analyzed vessels were significantly higher for iomeprol-400 (mean, 391.5–441.4 HU) compared with iodixanol-320 (mean, 332.3–365.5 HU, all $P \leq 0.0038$). There was no significant difference in qualitative visualization of coronary arteries (mean scores, 4.3–4.5 for iomeprol, 4.1–4.3 for iodixanol, $P = 0.15$–$0.28$), or in diagnostic confidence scores. HU were inversely correlated with the number of insufficiently opacified segments (all readers $P \leq 0.0006$).

**Conclusions:** The high-iodine concentration contrast medium iomeprol-400 demonstrated significant benefit for coronary arterial enhancement compared with the iso-osmolar contrast medium iodixanol-320 when administered at identical flow rates and volumes for coronary DS-CTA. In addition, higher enhancement levels were found to be associated with lower numbers of inadequately visualized segments. Finally, observed mean heart rate changes after intravenous contrast injection were generally small during the examination and comparable for both agents.

**Key Words:** Hounsfield units (HU), dual-source computed tomography, coronary arteries, heart rate, iomeprol, iodixanol

(*Invest Radiol* 2011;46: 457–464)

The primary goal of coronary computed tomography angiography (CTA) is to obtain sufficiently high-resolution images to facilitate accurate vascular diagnoses while maximizing patient safety and tolerability. As with other CTA applications, a high concentration of iodinated contrast media (CM) has been shown to be beneficial for coronary CTA, providing higher intra-arterial contrast attenuation and superior image quality.[1,2] Therefore, it might be anticipated that a CM with the highest iodine concentration available, such as iomeprol-400 (Iomeron-400; 400 mgI/mL, Bracco Imaging SpA. Milan, Italy) would be preferable for coronary CTA. However, intravascular dilution of CM can degrade vascular enhancement and therefore, it has been suggested that a CM that is iso-osmolar to plasma, such as iodixanol-320 (Visipaque-320, GE Healthcare, Chalfont St Giles, United Kingdom), might result in less dilution of intravascular fluid by influx from the extravascular space.[3]

The presence of artifacts, particularly those associated with cardiac motion, is another potential influence on the diagnostic quality of CTA images.[4] In detection of significant obstructing lesions in the coronary arteries, a higher heart rate was shown to result in decreased specificity.[5,6] In addition, because reliable electrocardiogram (ECG)-triggering in coronary CTA is critical to achieve high diagnostic image quality, it is also desirable to minimize fluctuations in heart rate.[7,8] During left ventriculography, ionic high-osmolar CM may cause an initial brief decrease in heart rate followed by a longer more pronounced increase, as well as a bradycardia beginning a few seconds after intracoronary injection.[9–12] Noninvasive CTA using intravenous (IV) injection of CM is probably associated with considerably smaller effects on cardiac function and rhythm compared with invasive cardioangiographic examinations, in which the undiluted CM is directly injected into the coronary arteries. Therefore, the findings from studies of intracoronary contrast injection cannot be directly extrapolated to CTA. However, the question has been raised as to whether CM characteristics such as iodine concentration, osmolarity, galenics, or pharmacokinetics of different compounds may affect the diagnostic quality of coronary CTA.

The aim of this study was to compare the high-iodine concentration, low-osmolar agent iomeprol-400 with the iso-osmolar CM iodixanol-320 at equal total volumes (mL) and equal flow rates (mL/s) for state-of-the-art coronary dual-source CTA (DS-CTA). Real predose heart rate values were measured during the nonen-

Received November 3, 2010, and accepted for publication, after revision, January 28, 2011.

From the *University Hospital of Munich Großhadern, Department of Radiology, Munich, Germany; †Hospital Niguarda Ca' Granda, Radiologia Sud, Milan, Italy; ‡University Hospital of Mannheim, Department of Radiology, Mannheim, Germany; §Hospital of Padova, Radiologia, Padova, Italy; ¶Hospital San Camillo-Forlanini, Diagnostica per immagini Cardioscienze, Rome, Italy; ‖Hospital Policlinico San Matteo, Radiologia, Pavia, Italy; **Hospital Maggiore Policlinico, Unità Operativa Radiologia, Milan, Italy; ††University Hospital of Erlangen, Department of Radiology, Erlangen, Germany; ‡‡Bracco Imaging, Konstanz, Germany; and §§University Hospital of Messina, UO Diagnostica per Immagini e Radioterapia - Scienze Radiologiche, Messina, Italy.

Supported by a grant from Bracco Imaging SpA, Milan, Italy.

Reprints: Christoph R. Becker, MD, University Hospital of Munich, Großhadern, Institute for Clinical Radiology, Marchioninistr 15, D- 81377 München, Germany. E-mail: christoph.becker@med.uni-muenchen.de.



ISSN: 0020-9996/11/4607-0457

hanced calcium scoring scans. By analyzing the vascular enhancement, vessel delineation, overall diagnostic quality, and effect on heart rate, the effect of the specific properties of these 2 agents on the quality of coronary DS-CTA examinations was assessed and compared.

## MATERIALS AND METHODS

### Study Design

This study was a multicenter, randomized, double-blind, parallel-group comparison conducted according to Guidelines of Good Clinical Practice with individual institutional review board approval. Six sites in Italy and 3 sites in Germany participated in this trial. All patients provided written informed consent prior to enrollment. The lead author (C.R.B.) had complete access to the results of the study, and all authors had control of the data and statistical results included in this report.

### Subjects

Adult patients (age, ≥18 years) weighing less than 150 kg, and scheduled for coronary CTA and coronary calcium score examinations because of suspicion of coronary artery disease were eligible for inclusion. Patients were excluded from the study for the following factors: if they had a history of hypersensitivity to iodinated contrast agents; had known or suspected hyperthyroidism or pheochromocytoma; had renal impairment (eGFR, <60 mL/min/1.73 $m^2$ or SCr, >1.5 mg/dL); had atrial fibrillation or any other cardiac arrhythmia that would preclude reliable ECG gating; had severe congestive heart failure (New York Heart Classification IV); was a pregnant or lactating female; or had received an iodinated contrast agent within 7 days or any investigational compound within 30 days before enrollment into the study. Additionally, investigators excluded patients who had peripheral vein conditions that would not allow for the required fast administration of contrast agents or who had a calcium score that in the opinion of the investigator was too high to obtain diagnostic images.

### CM Administration

After enrollment into the study, patients were randomly assigned to receive either iodixanol-320 (Visipaque 320, GE Healthcare, Giles St Chalfont, United Kingdom; 320 mg iodine per mL) or iomeprol-400 (Iomeron 400, Bracco Imaging SpA, Milan, Italy; 400 mg iodine per mL). A drug dispensing professional at each center managed the preparation, dispensing, and accountability of the contrast agents. To ensure study blinding, this person did not participate in any study assessments or evaluations. Study CM were warmed to body temperature and administered by dual-head (contrast/saline) power injection into a peripheral vein of the right arm by mean of an 18G or larger venous-catheter. The patients in the iodixanol-320 group were administered 80 mL of contrast medium (25.6 g iodine) that was injected intravenously at 5 mL/s followed by a 40 mL saline flush, corresponding to an injection duration of 16 seconds and an iodine flux of 1.6 gI/s. The patients in the iomeprol-400 group were administered 80 mL of contrast medium (32.0 g iodine) also injected intravenously at a rate of 5 mL/s, followed immediately by a 40-mL flush of physiological saline (0.9% NaCl solution) injected at the same flow rate, corresponding to an injection duration of 16 seconds and an iodine flux of 2.0 gI/s.

### MDCT Angiography

All patients underwent CTA with a 64-slice dual-source CT scanner (Somatom Definition, Siemens Healthcare, Erlangen, Germany).[13,14] To minimize variability and improve the assessment of the contrast agent effect, each site used a standardized protocol for the CT examination that included: chest scout image, cephalocaudal scan direction; CARE bolus triggering in descending aorta with 100 HU trigger + 4 seconds; retrospective ECG gating with ECG dose modulation, 120 kVp tube voltage, and 330 milliseconds gantry rotation. Image reconstruction was performed at least at 3 different ECG intervals (usually including best diastole and best diastole) with a slice thickness of 0.6 mm, reconstruction interval of 0.3 mm, and a standard reconstruction algorithm (B26).

### Safety Assessments

A medical history and physical examination were taken at the time of entry into the study. Any concomitant medications administered with 24 hours before, during, or within 2 hours after the CT examination were noted. All patients were monitored for adverse events from the time of their enrollment into the study until 2 hours after CM exposure. Investigators were asked to categorize any adverse events observed as serious or not serious, and within the nonserious category as mild, moderate, or severe. Investigators also categorized the relationship of any adverse events to CM administration (probably related, possibly related, not related, unknown relationship).

### Heart Rate

No beta-blockers or nitrates were given specifically for coronary DS-CTA scanning; however, a record was made of any subjects who were already on beta-blockade and/or nitrate therapy for their underlying cardiovascular condition. Heart rates were assessed and documented using the Siemens Somatom Definition scanner tools and software (Syngo CT 2007 or Syngo CT 2008). The minimum, maximum, and mean heart rates were measured at 2 time points: predose (ie, the time during which the CT scanner monitors the cardiac rhythm during the calcium scoring scan) and postdose (ie, the time during which the CT scanner monitors the cardiac rhythm during the coronary CTA scan).

### Coronary Artery Segmentation

For the CTA assessment of the coronary arteries, the following 17-segment model (based on the standard 15-segment model of the American Heart Association) was used:[15]

Right coronary artery (RCA): (1) proximal RCA, (2) mid RCA, (3) distal RCA, (4a) right posterior descending, (4b) atrioventricular node,

Left main coronary artery (LM): segment (5),

Left anterior descending artery (LAD): (6) proximal LAD, (7) mid LAD, (8) distal LAD (including left posterior descending, if present), (9) first diagonal, (10) second diagonal,

Left circumflex artery (LCX): (11) proximal LCX, (12) obtuse marginal, (13) mid LCX, (14) posterolateral, (15) distal LCX/left posterior descending, (16) ramus intermedius (if present).

### Efficacy Assessments

All efficacy assessments, including technical adequacy of images, were performed off-site by 3 independent since 7 to 17 years board-certified radiologists, familiar with cardiovascular imaging, and unaffiliated with any of the study institutions. Readers were fully blinded to all clinical and other radiologic subject information. Coronary CTA subject image sets were evaluated from 1 randomized pool of postprocessed subject image sets. The 3 CTA readers independently evaluated the coronary CTA image sets in terms of technical adequacy, contrast opacification, and overall and segmental qualitative assessments. Image sets were first reviewed for technical adequacy. If the reader determined that the entire image set was not technically adequate, no further assessment was performed, and the reader attributed the inadequacy to one of the following: subject motion (body, and/or respiratory, and/or cardiac), other artifact (eg, metallic), insufficient radiation dose (ie, images too noisy), or other.

### Quantitative Efficacy Assessments

Contrast opacification (in Hounsfield units [HU]) was measured by the 3 blinded readers using circular regions of interest (ROIs) manually placed in the following areas: midportion of LM, segment 5 (ROI as large as appropriate); midportion of RCA, segment 1 (ROI as large as appropriate); lumen of the left ventricle (1 cm ROIs at 3 different positions along the longitudinal axis); ascending aorta (1 cm ROI mid-lumen); and mediastinal tissue, next to the aortic ROI (extraluminal, extrapulmonary ROI as large as appropriate).

### Qualitative Efficacy Assessment

General visual assessment of contrast enhancement and delineation of anatomic structures, particularly taking into account the smaller coronary artery segments, was evaluated using the following 5-point scale:

1 = Insufficient (incomplete opacification and delineation of the proximal coronary artery segments);

2 = Poor (complete visualization of the proximal coronary artery segments; generally poor visualization of mid to distal coronary artery segments);

3 = Fair (complete visualization of the proximal coronary artery segments; partial visualization of mid to distal coronary artery segments);

4 = Good (complete visualization of the proximal, mid and distal major coronary artery segments; subsegmental arteries not sufficiently assessable); and

5 = Excellent (complete visualization of the proximal, mid and distal major coronary artery segments; subsegmental arteries sufficiently assessable).

Diagnostic confidence (ie, trust in the delineation of pathologic findings) was assessed based on the following scores:

1 = Insufficient (adequate diagnostic assessment of coronary artery disease not possible);

2 = Poor (overall confidence in the diagnosis of pathologic findings in coronary arteries low);

3 = Fair (confidence in the diagnosis of pathologic findings in coronary arteries moderate);

4 = Good (good and almost full, though perhaps time-consuming assessment, with a high confidence in diagnosis);

5 = Excellent (rapid and easy assessment of coronary segments with a high diagnostic confidence).

For the assessment of vessel delineation of coronary artery segments, each reader assessed whether each of the 17 coronary artery segments was visualized to a quality that is adequate for accurate diagnosis of the presence and severity of stenosis (yes/no). An adequate quality for the accurate diagnosis of the presence and severity of coronary artery stenosis comprised 2 basic features: (1) no more than mild blurring of the spatial distinction between the vessel wall and lumen, and (2) a readily visible distinction in image contrast between calcified plaque, enhanced vessel lumen, and noncalcified vessel wall or plaque. If the vessel delineation was considered inadequate for a segment, the reason was specified as one or more of the following: insufficient vessel opacification, cardiac motion artifacts, extracardiac motion artifacts, the presence of plaques (calcified, not calcified), the presence of stents, vessel diameter $\leq$1.5 mm, occlusion, anatomically absent, or other.

### Statistical Analysis

The sample size of 48 patients per treatment arm was determined based on 90% power to discriminate between HU after the 2 regimens, and assuming a 10% attrition rate. The computation software nQuery Advisor 6.01 was used for sample size calculation. Comparisons of demographic parameters (gender, age, weight, height) and calcium scoring data between patients in the iomeprol and iodixanol groups were performed using Student *t* test for continuous variables and the $\chi^2$ test for categorical variables. Changes in heart rates (mean, minimum, maximum, and maximum-minimum) between predose (baseline value) and postdose measurements were compared using the 2-sample *t* test. The mean contrast density in the ROIs was compared between the 2 treatment arms using the analysis of covariance model with the SD of the ROI as covariate. Evaluable coronary segments were expressed as a number and as a percentage of the total number of eligible segments, and were compared between treatment arms using the $\chi^2$ test. Image quality was assessed by the mean scores of visualization of vessels and diagnostic confidence. Two-sided 95% confidence intervals for the differences of the mean scores between the treatment groups were calculated and the 2 treatment groups were compared using the 2-sample *t* test. Inter-reader agreement for vessel delineation was evaluated using generalized kappa statistic as well as percentage agreement. A regression analysis was performed on the basis of the number of inadequately visualized segments due to insufficient vessel opacification, and also due to anatomically absent, $\leq$1.5 mm, or occluded segments as response variable; and treatment group and HU as explanatory variables. All statistical tests were conducted at a significance level of $P \leq 0.05$ using the statistical software package SAS version 8.2 (SAS Institute Inc, Cary, NC).

## RESULTS

### Study Population

Of the 107 patients enrolled in the study, 104 (97.2%) were given randomized contrast agent (54 in the iomeron group, 50 in the iodixanol group). Of these patients, 96 (92.3%) underwent CTA without major protocol violation and thus were included in the efficacy population, including 49 patients in the iomeprol-400 group and 47 in the iodixanol-320 group. Complete heart rate data could be collected from 50 patients in the iomeprol-400 group and from 46 patients in the iodixanol-320 group. No significant differences were found between the iomeprol-400 and iodixanol-320 treatment groups in terms of mean patient age (60.4 vs. 57.0 years, respectively), mean patient height (169.0 vs. 170.2 cm, respectively), and mean patient weight (78.0 vs. 77.4 kg, respectively) (Table 1). No significant difference was found for the calcium scores in the iomeprol-400 group (Agatston score, 174 $\pm$ 344) compared with the iodixanol-320 group (Agatston score, 232 $\pm$ 499; $P = 0.50$). No meaningful differences were noted between the 2 study populations in terms of medical history, physical examinations, or concomitant medication administration. Twenty-three patients (42.6%) were under previous beta-blockage in the iomeron-400 group compared with 21 patients (42%) in the iodixanol-320 group. No adverse events were recorded for any patient during the study period.

**TABLE 1.** Patient Demographic Characteristics

| Characteristic | Iomeprol-400 (N = 54) | Iodixanol-320 (N = 50) | *P* |
|---|---|---|---|
| Gender (% male) | 31 (57.4%) | 28 (56.0%) | 0.8849 |
| Age (yr), mean $\pm$ SD | 60.4 $\pm$ 11.6 | 57.0 $\pm$ 11.2 | 0.1323 |
| Height (cm), mean $\pm$ SD | 169.0 $\pm$ 9.2 | 170.2 $\pm$ 9.8 | 0.5158 |
| Weight (kg), mean $\pm$ SD | 78.0 $\pm$ 19.1 | 77.4 $\pm$ 17.7 | 0.8707 |
| Any concomitant medication, N (%) | 39 (72.2) | 40 (80.0) | 0.3537 |
| Beta blocker medications, N (%) | 23 (42.6) | 21 (42.0) | 0.3521 |

SD indicates standard deviation; N, number of patients.

## Heart Rate Changes

No significant differences (all $P > 0.1$) were observed between the iomeprol-400 and iodixanol-320 groups, neither between predose (baseline) or postdose values (Fig. 1), nor between changes from pre- to postdose for the tested parameters mean, maximum, and minimum heart rate (Table 2). However, mean heart rate was already slightly higher before contrast injection (baseline) in the iomeron-400 group (68.1 ± 15.86 bpm) compared with those in the iodixanol-320 group (66.5 ± 14.26 bpm) and remained slightly higher at postdose (69.8 ± 16.57 bpm vs. 66.0 ± 13.88 bpm, n.s.). Similarly, minimum and maximum heart rate, as well as the intragroup variations of all heart rate values expressed by the SD, was already slightly higher in the iomeron-400 group before the contrast agent injection. Overall, mean changes of the heart rate values from

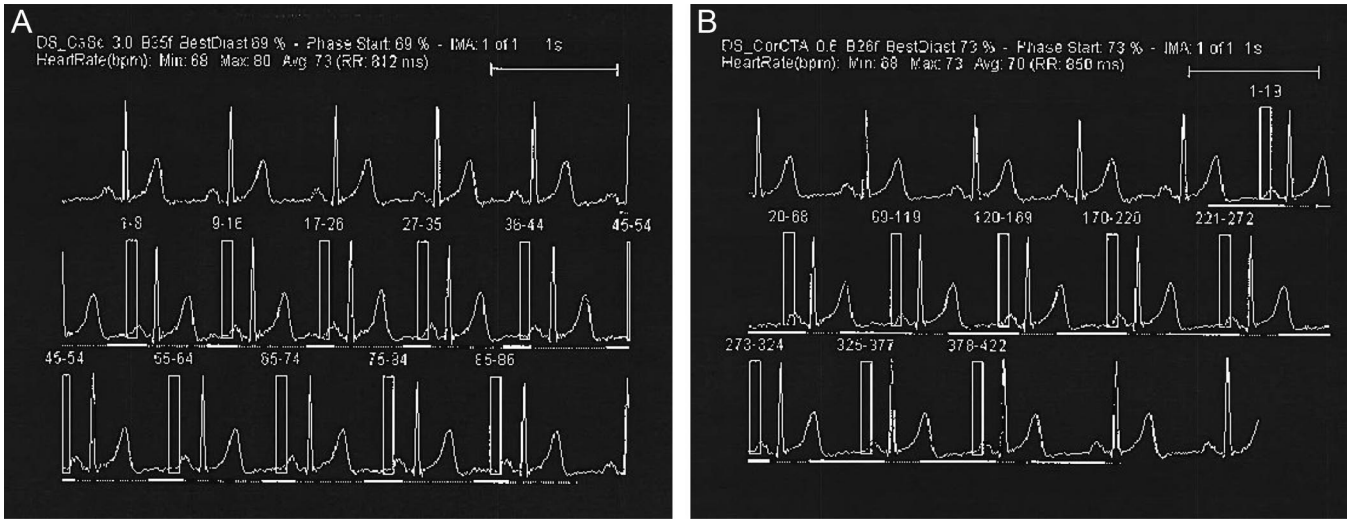


**FIGURE 1.** Example of a pre- and postdose ECG (minimum, maximum, and mean heart rate) recorded by the DS-CT during the calcium scoring scan (A) as well as during the contrast-enhanced coronary CT angiography (B).

**TABLE 2.** Pre- and Postdose Heart Rate Measurements

| | Predose | Postdose | Change From Baseline | *P* |
|---|---|---|---|---|
| Mean heart rate (bpm) | | | | |
| Iomeprol-400 (N) | 50 | 50 | 50 | 0.1195 |
| Mean (SD) | 68.1 (15.86) | 69.8 (16.57) | 1.7 (7.67) | |
| Iodixanol-320 (N) | 47 | 47 | 47 | 0.5547 |
| Mean (SD) | 66.5 (14.26) | 66.0 (13.88) | −0.5 (5.88) | |
| *P* | 0.6151 | 0.2279 | 0.1131 | |
| Minimum heart rate (bpm) | | | | |
| Iomeprol-400 (N) | 50 | 50 | 50 | 0.1007 |
| Mean (SD) | 63.0 (15.53) | 65.2 (17.16) | 2.2 (9.47) | |
| Iodixanol-320 (N) | 46 | 47 | 46 | 0.3807 |
| Mean (SD) | 61.5 (12.86) | 62.6 (13.69) | 0.9 (6.99) | |
| *P* | 0.6140 | 0.4053 | 0.4344 | |
| Maximum heart rate (bpm) | | | | |
| Iomeprol-400 (N) | 50 | 50 | 50 | 0.9808 |
| Mean (SD) | 76.2 (17.82) | 76.1 (19.28) | −0.04 (11.70) | |
| Iodixanol-320 (N) | 46 | 47 | 46 | 0.1864 |
| Mean (SD) | 72.5 (15.76) | 71.1 (14.63) | −1.6 (8.24) | |
| *P* | 0.2909 | 0.1543 | 0.4406 | |
| Maximum−minimum heart rate (bpm) | | | | |
| Iomeprol-400 (N) | 50 | 50 | 50 | 0.1754 |
| Mean (SD) | 13.2 (13.69) | 10.9 (15.09) | −2.3 (11.73) | |
| Iodixanol-320 (N) | 46 | 47 | 46 | 0.0229 |
| Mean (SD) | 11.0 (6.85) | 8.5 (5.20) | −2.5 (7.32) | |
| *P* | 0.3215 | 0.2998 | 0.8944 | |

SD indicates standard deviation; N, number of patients..

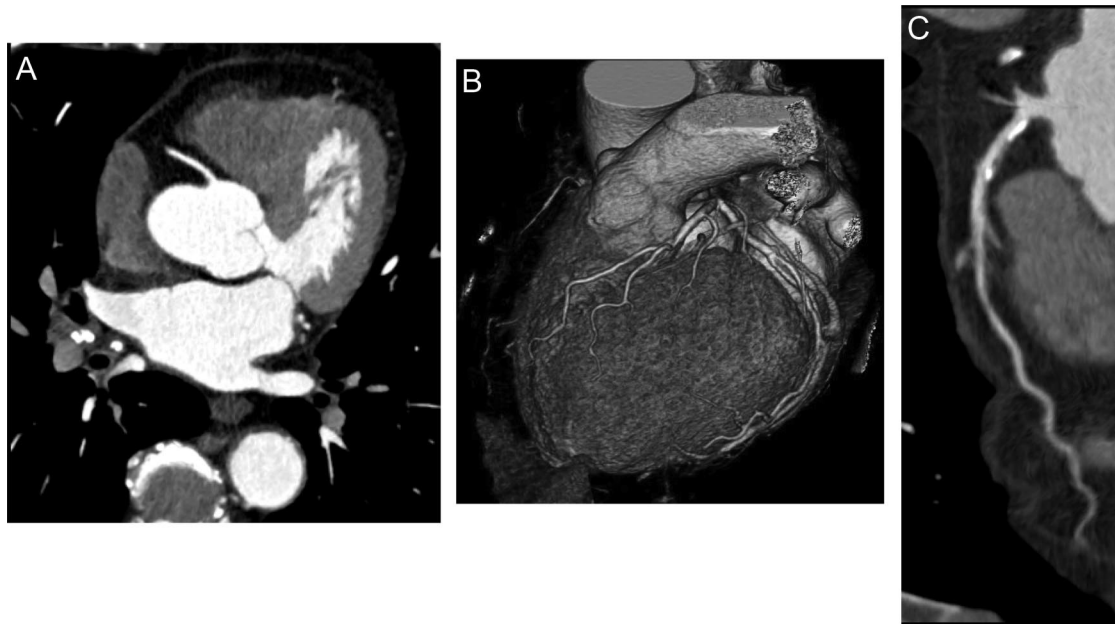


**FIGURE 2.** Coronary CTA with iomeron 400 (80 mL, 5 mL/s) of a 70-year-old man (BMI, 26.3 kg/m$^2$) with high coronary arterial enhancement (mean, 482–524 HU), and excellent quality scores (5 of 5, for all 3 readers) for vessel visualization and diagnostic confidence. The readers assessed 17, 17, and 16 vessel segments, respectively, out of 17 as adequately delineated. A, axial slice; B, VR image; C, curved multiplanar reformat of the LAD artery. Note that due to the high contrast, the window width and level could be increased (1000 HU, 300 HU) with an excellent depiction of calcified and noncalcified plaques.

pre- to postdose were generally small (largest observed mean difference: + 2.2 bpm). In addition, the change in heart rate fluctuation measured as Δ = maximum − minimum heart rate was not statistically significantly different between iomeprol-400 and iodixanol-320 ($P = 0.8944$). In both groups, even a reduction of the heart rate variability was observed after contrast injection compared with baseline. The mean change from pre- to postdose for Δ was −2.3 bpm for iomeron-400 ($P = 0.1754$) and −2.5 bpm for iodixanol-320 ($P = 0.0229$).

### Contrast Density Measurements

Highly significant differences were observed between the iomeron-400 group (Fig. 2) and the iodixanol-320 group (Fig. 3) in contrast density measurements (HU) of the left main and right coronary arteries by all 3 readers (Table 3). Measured mean enhancements of the coronary arteries were 433.0 to 441.4 HU for iomeron-400 compared with 354.6 to 365.5 HU for iodixanol-320 ($P \leq 0.0038$ for all 3 readers). Similar statistically significant results were observed by all readers for the aorta and left ventricle.

### Vessel Delineation

The percentage of adequately visualized segments, including those with insufficient vessel opacification, cardiac motion artifacts, extracardiac motion artifacts, plaques (calcified, not calcified), stents, anatomically absent, diameter ≤1.5 mm, occlusion, and other, was comparable between the 2 treatment groups, with no statistically significant differences noted for each of the 3 readers (Table 4). One hundred percent agreement was achieved between 2 out of 3 off-site readers, 66% and 67% agreement was achieved between all 3 readers for the iomeron-400 group and the iodixanol-320 group, respectively. The generalized kappa values were 0.335 and 0.366 respectively.

The regression analysis showed that HU, but not contrast agent group, negatively correlated with the number of inadequately visualized segments due to insufficient vessel opacification, anatomically absence, small size, or occlusion and was statistically significant for all 3 readers ($P < 0.0001$, $P = 0.0006$, and $P < 0.0001$, for readers 1, 2, and 3, respectively). Similar highly significant results were found ($P < 0.0001$, $P < 0.0002$, $P < 0.0001$ for the 3 readers) in an analog of regression analysis with only insufficient vessel opacification as response variable, suggesting that higher HU correlate with lower numbers of inadequately visualized segments.

### Qualitative Assessment

There was no significant difference in overall diagnostic confidence scores between the iomeprol-400 group and the iodixanol-320 group (for the 3 readers mean scores of 4.1–4.2 for iomeprol and 4.1–4.3 for iodixanol, $P = 0.57$–$0.84$) (Table 5). Mean scores for qualitative visualization of coronary arteries tended to be higher in the iomeprol-400 group; however, statistical significance was not observed (for the 3 readers mean scores of 4.3–4.5 for iomeprol and 4.1–4.3 for iodixanol, $P = 0.15$–$0.28$). Overall, the subjective, qualitative assessment was similar for both treatment groups.

## DISCUSSION

### Vessel Enhancement

A highly significant difference was observed in HU values between iomeprol-400 and iodixanol-320 for all readers and all analyzed coronary arterial regions, demonstrating benefit for higher iodine concentration CM when administered at identical flow rates and volumes for coronary DS-CTA. These findings offer evidence that CM characteristics such as iso-osmolality or the presence of calcium ions do not compensate for the lower iodine concentration of a dimeric contrast agent in terms of arterial enhancement in HU as compared with a low-osmolar, monomeric contrast agent with high iodine concentration. Our study confirms that rather the iodine delivery rate is the critical parameter for contrast enhancement

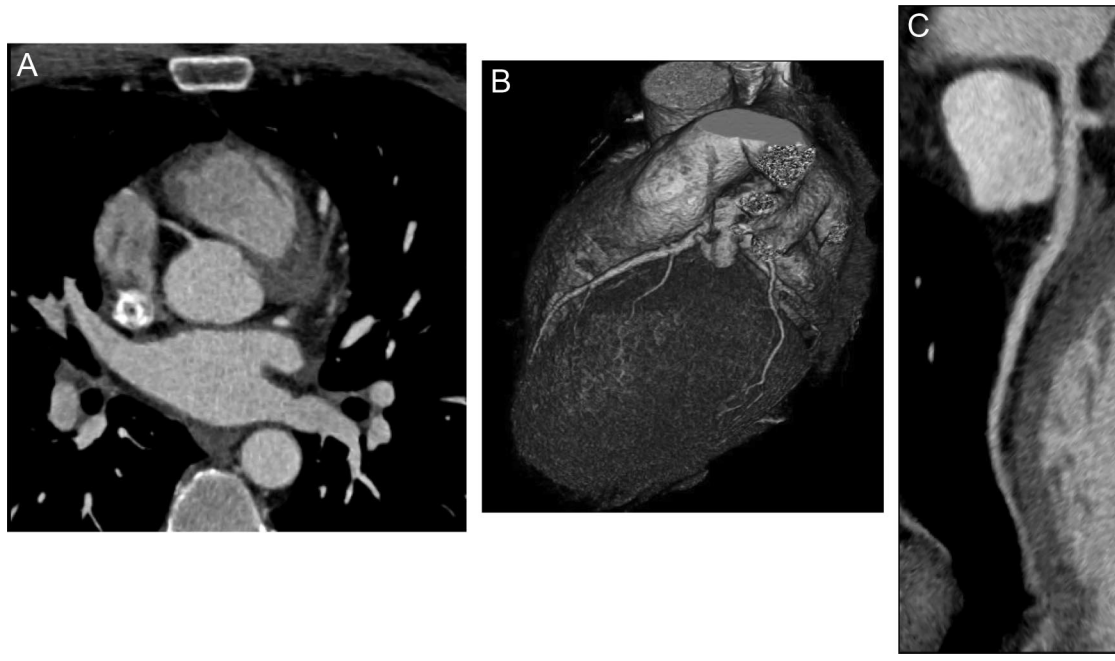


**FIGURE 3.** Coronary CTA with iodixanol 320 (80 mL, 5 mL/s) of a 45-year-old man (BMI, 25.7 kg/m$^2$) with only moderate coronary arterial enhancement (mean, 310–322 HU), and good quality scores (4 of 5, for all 3 readers) for vessel visualization and diagnostic confidence. Of 17 vessel segments the readers assessed only 14, 10, or 13, respectively, as adequately delineated. A, axial slice; B, VR image; C, curved multiplanar reformat of the LAD artery.

**TABLE 3.** Mean Contrast Densities in the Combined Left Main/Right Coronary Arteries, Left Ventricle, and Ascending Aorta

| | Reader 1 | | Reader 2 | | Reader 3 | |
|---|---|---|---|---|---|---|
| **Region-of-Interest** | **Iomeprol-400** | **Iodixanol-320** | **Iomeprol-400** | **Iodixanol-320** | **Iomeprol-400** | **Iodixanol-320** |
| Left main/right coronary arteries combined | | | | | | |
| Number evaluated | 46 | 44 | 47 | 45 | 49 | 47 |
| Contrast density (HU), mean ± SD | 439.96 ± 87.20 | 362.06 ± 80.00 | 441.38 ± 99.85 | 365.47 ± 76.58 | 433.08 ± 92.78 | 354.59 ± 81.73 |
| *P* | 0.0001 | | 0.0031 | | 0.0038 | |
| Left ventricle | | | | | | |
| Number evaluated | 46 | 44 | 47 | 45 | 49 | 47 |
| Contrast density (HU), mean ± SD | 407.71 ± 81.39 | 344.59 ± 69.01 | 401.75 ± 82.70 | 341.09 ± 68.36 | 391.51 ± 84.25 | 332.28 ± 73.42 |
| *P* | 0.0001 | | 0.0003 | | 0.0008 | |
| Ascending aorta | | | | | | |
| Number evaluated | 46 | 44 | 47 | 45 | 49 | 47 |
| Contrast density (HU), mean ± SD | 431.68 ± 82.34 | 354.28 ± 69.95 | 431.06 ± 85.58 | 352.93 ± 68.01 | 427.93 ± 87.26 | 351.49 ± 74.28 |
| *P* | <0.0001 | | <0.0001 | | <0.0001 | |

Average from 3 locations in the left ventricle.
SD indicates standard deviation; HU, Hounsfield units.

optimization in arterial phase examinations such as coronary CTA, which can be maximized using high iodine concentration CM.[16]

Despite the significantly higher HU values obtained with iomeprol-400, no statistically significant difference was noted between the groups in terms of any of the qualitative assessments, including vessel delineation (segment level), general vessel visualization, and diagnostic confidence, for any of the 3 readers. One explanation for these results is that the qualitative image quality assessment of the readers was influenced more by factors such as motion artifacts, image noise, or calcium burden of the coronary arteries, and that contrast enhancement per se played only a minor role in this subjective evaluation. This may reflect the general experience in CT that enhancement in high-contrast examinations such as CT angiography may only be considered inadequate in case of wrong scan to contrast timing or injection failure. However, a regression analysis based on the number of segments with insuffi-

**TABLE 4.** Segment Level Qualitative Assessments: Vessel Delineation

| | Reader 1 | | Reader 2 | | Reader 3 | |
|---|---|---|---|---|---|---|
| **Characteristic** | **Iomeprol-400** | **Iodixanol-320** | **Iomeprol-400** | **Iodixanol-320** | **Iomeprol-400** | **Iodixanol-320** |
| No. coronary segment evaluated | 782 | 748 | 799 | 765 | 833 | 799 |
| Adequately visualized vessel segments, N (%) | 642 (82.1) | 616 (82.4) | 616 (77.1) | 587 (76.7) | 599 (71.9) | 579 (72.5) |
| Inadequately visualized vessel segments, N (%) | 140 (17.9) | 132 (17.6) | 183 (22.9) | 178 (23.3) | 234 (28.1) | 220 (27.5) |
| *P* | 0.8959 | | 0.8643 | | 0.8019 | |

**TABLE 5.** Image Quality Scores for Diagnostic Confidence and Visualization of Coronary Arteries

| | Iomeprol-400 | | Iodixanol-320 | | |
|---|---|---|---|---|---|
| | **Mean ± SD** | **Median (Range)** | **Mean ± SD** | **Median (Range)** | ***P*** |
| Visualization | | | | | |
| Reader 1 | 4.5 ± 0.86 | 5 (2, 5) | 4.3 ± 0.94 | 5 (2, 5) | 0.28 |
| Reader 2 | 4.5 ± 0.86 | 5 (2, 5) | 4.3 ± 0.71 | 4 (3, 5) | 0.28 |
| Reader 3 | 4.3 ± 0.80 | 4 (2, 5) | 4.1 ± 0.84 | 4 (2, 5) | 0.15 |
| Diagnostic confidence | | | | | |
| Reader 1 | 4.2 ± 0.85 | 4 (2, 5) | 4.3 ± 0.86 | 5 (2, 5) | 0.57 |
| Reader 2 | 4.2 ± 0.82 | 4 (2, 5) | 4.3 ± 0.73 | 4 (2, 5) | 0.65 |
| Reader 3 | 4.1 ± 1.01 | 4 (1, 5) | 4.1 ± 0.82 | 4 (2, 5) | 0.84 |

SD indicates standard deviation: based on a 5-point scale.

cient vessel opacification, anatomically absent, ≤1.5 mm, or occluded segments as response variable; treatment group and HU as explanatory variables demonstrated that HU was negatively correlated with the number of insufficiently visualized segments. This indicates that when greater contrast was achieved (higher HU), fewer segments were insufficiently visualized or considered anatomically absent. The analysis was statistically significant for all 3 readers. For obvious reasons, the number of visualized coronary artery segments may be considered a relevant image quality criterion for coronary CTA. As this result was based on a semi-quantitative assessment, it may be less subjective compared with the image quality scores used for the qualitative evaluation of vessel visualization. Subjective image quality scores alone may not be sufficient for such comparisons,[17] especially in complex situations such as in coronary CTA, where reader's primary evaluation can be influenced more by several other factors than just by vessel enhancement only.

## Heart Rate Changes

In the past, several studies have investigated effects of intra-arterial application of CM on heart function. Following experimental studies showing that a measured transient depression of left ventricular pressure was essentially abolished after addition of calcium to the CM,[18] calcium was added to iodixanol, both to provide normal osmolality and to reduce hemodynamic effects.[19,20] Additional animal studies showed that such hemodynamic effects seen with other low-osmolar agents may be attributable to the addition of calcium-chelating agents such as EDTA[21]; however, iomeprol does not contain EDTA and therefore, may not be expected to cause comparable negative inotropic effects. Generally, with injections of nonionic iodinated CM, the chronotropic changes observed are smaller.[22] However, there may be differences in effects on heart rate and related artifacts among nonionic CM: in a preclinical study, intra-arterial injection of the iso-osmolar, calcium-containing contrast agent iodixanol demonstrated less influence on heart rate compared with another nonionic low-osmolar agent, iopromide[23] while more recently, no difference in effect on heart rate between iomeprol and iodixanol was demonstrable after intra-arterial or intracardiac injection.[22]

In our study, no significant differences between contrast agent groups in terms of heart rate changes were observed after coronary CTA with IV administration of CM: the observed changes in mean, minimum, and maximum heart rate from pre- to postdose were small and clinically inconsequential. Similarly, no differences were found between contrast agent groups in the maximum-minus-minimum heart rate from pre- to postdose, a parameter that reflects heart rate variability. This value even decreased after contrast injection compared with baseline measurement for both contrast agents. It can be concluded that, for coronary DS-CTA, IV injection of either iomeprol-400 or iodixanol-320 is not associated with clinically relevant changes in heart rate, and that there is no difference in effects on heart rate between the 2 agents.

A recently published study has come to a different conclusion[24]: Svensson et al concluded that iodixanol-320 caused less heart arrhythmia in coronary CTA than iomeprol-400, because they found more deviations from a predefined scanning protocol in the postdose heart rate values for the iomeron-400 group. However, in this study subjective heart rate categories with arbitrarily defined thresholds were chosen for identification of heart rate changes. Furthermore, data of predose heart rates were not provided. Therefore, it is not possible to analyze whether differences in the heart rate existed already before contrast injection, which would have influenced their observed postdose differences between iomeron-400 and iodixanol-320. For example, we have measured a slightly higher heart rate (n.s.) already before contrast injection in the patient group who later received iomeprol-400 in our study. We believe that primarily changes from pre- to postdose should be assessed to evaluate potential effects of contrast medium application on the heart rate. In our study, true baseline heart rate values were measured during a calcium scoring scan. This kind of crossover placebo examination (nonenhanced scan) provides useful information about heart rate changes, because other potentially relevant, but nondrug-related influences (breath hold, Valsalva effect, patient agitation during the examination) are covered by this baseline measurement. Furthermore, it was not stated by Svensson et al how many patients were taking beta-blockers and whether there were differences between the groups. In our study, no beta-blockers or nitrates were given specifically for coronary CTA scanning to avoid heart rate effects related to these drugs. Of our patients, 42% were on beta-blocker therapy, but there was no imbalance between the iomeron-400 and the iodixanol-320 group in the proportion of patient on beta-blockers. Finally, Svensson et al reported several different evaluations of the patients' heart rate; however, it was not reported if multiplicity adjustment was performed, which would reduce the number of *P* values, which reached significance. The probably clinically most relevant end point "number of

patients with changes in heart rate interfering with the predefined scan protocol" was not only not significantly different, but in fact almost identical (31/50 = 62% vs. 32/50 = 64%). In summary, it seems that our results and the results obtained by Svensson et al are not so different but rather similar. It is merely the conclusion set by Svensson et al, which is markedly different.

## Limitations

Taking into consideration the different reasons for inadequate vessel delineation, the most prominent across the 3 readers was anatomic absence, followed by cardiac motion artifacts and insufficient vessel opacification. Extracardiac motion (which might be caused by pain or heat sensation) was not a relevant reason, and was found only in 3 patients in both groups by only 1 reader. A clear limitation of our study is that no gold standard such as coronary angiography was available that could have confirmed or refuted the assessment of the readers. The percentage of coronary segments, which were adequately delineated, was relatively low in both groups for all readers (72%–82%) compared with previous publications.[24–27] This may be in part because lacking a gold standard, a vessel might be judged as being absent, however detectable by angiography because of higher spatial and contrast resolution. Thus, vessel segments assessed with a diameter $<1.5$ mm or segments assessed as anatomically absent were scored as inadequately visualized. This assumption was made to minimize bias when comparing the 2 study agents, but decreased the overall percentage of adequately delineated vessel segments. Further studies are needed to evaluate the clinical relevance of the observed inverse correlation between contrast enhancement and number of inadequately visualized coronary artery segments.

Another limitation of our study and of the study by Svensson et al was that the iodine dose and delivery rate were different in both groups. A primary aim of our study was to clarify that iso-osmolality of iodixanol-320 does not compensate for the higher iodine concentration used in the low-osmolar iomeprol-400 group. This hypothesis could clearly be rejected. However, we therefore needed to use identical volumes and flow rates. It may limit the evaluation of heart rate changes caused by administration of the different contrast agents. Adverse events, such as nephrotoxic effects, are often dose correlated which may also apply to effects on cardiac function. Thus, actually, the low-osmolar iomeprol-400 was disadvantaged regarding the evaluation of related heart rate changes as a higher iodine dose and delivery rate was used in this group compared with iodixanol-320. However, even with this disadvantage, no significant differences in heart rate were found in both groups, which may underline our conclusions about heart rate changes after IV contrast injection.

## CONCLUSION

The use of iomeprol-400 provided a significantly higher arterial enhancement in coronary DS-CTA compared with iodixanol-320 when administered at identical volumes and flow rates. In addition, higher enhancement levels were found to be associated with lower numbers of inadequately depicted segments. Finally, observed heart rate changes after IV contrast injection were generally small during the examination and comparable for both agents.

## REFERENCES


1. Cademartiri F, de Monye C, Pugliese F, et al. High iodine concentration contrast material for noninvasive multislice computed tomography coronary angiography: iopromide 370 versus iomeprol 400. *Invest Radiol*. 2006;41:349–353.
2. Cademartiri F, Mollet NR, van der Lugt A, et al. Intravenous contrast material administration at helical 16-detector row CT coronary angiography: effect of iodine concentration on vascular attenuation. *Radiology*. 2005;236:661–665.
3. Klow NE, Jacobsen EA, Refsum H. Cardioangiography and the hemodynamic effects of iodixanol. *Acta Radiol Suppl*. 1995;399:93–99.
4. Achenbach S, Anders K, Kalender WA. Dual-source cardiac computed tomography: image quality and dose considerations. *Eur Radiol*. 2008;18:1188–1198.
5. Cademartiri F, Mollet NR, Runza G, et al. Diagnostic accuracy of multislice computed tomography coronary angiography is improved at low heart rates. *Int J Cardiovasc Imaging*. 2006;22:101–105.
6. Rist C, Johnson TR, Becker CR, et al. New applications for noninvasive cardiac imaging: dual-source computed tomography. *Eur Radiol*. 2007;17(suppl 6):F16–F25.
7. Husmann L, Herzog BA, Burkhard N, et al. Body physique and heart rate variability determine the occurrence of stair-step artifacts in 64-slice CT coronary angiography with prospective ECG-triggering. *Eur Radiol*. 2009;19:1698–1703.
8. Brodoefel H, Burgstahler C, Tsiflikas I, et al. Dual-source CT: effect of heart rate, heart rate variability, and calcification on image quality and diagnostic accuracy. *Radiology*. 2008;247:346–355.
9. Dawson P, Cosgrove DO, Grainger RG. *Textbook of Contrast Media*. London, England: Taylor & Francis, Inc; 1999.
10. Spataro RF, Katzberg RW, Fischer HW, et al. High-dose clinical urography with the low-osmolality contrast agent Hexabrix: comparison with a conventional contrast agent. *Radiology*. 1987;162:9–14.
11. Klinke WP, Grace M, Miller R, et al. A multicenter randomized trial of ionic (ioxaglate) and nonionic (iopamidol) low osmolality contrast agents in cardiac angiography. *Clin Cardiol*. 1989;12:689–696.
12. Werner GS, Schmidt T, Scholz KH, et al. Comparison of hemodynamic and Doppler echocardiographic effects of a new low osmolar nonionic and a standard ionic contrast agent after left ventriculography. *Cathet Cardiovasc Diagn*. 1994;33:11–19.
13. Flohr TG, McCollough CH, Bruder H, et al. First performance evaluation of a dual-source CT (DSCT) system. *Eur Radiol*. 2006;16:256–268.
14. Rist C, Johnson TR, Müller-Starck J, et al. Noninvasive coronary angiography using dual-source computed tomography in patients with atrial fibrillation. *Invest Radiol*. 2009;44:159–167.
15. Mollet NR, Cademartiri F, Nieman K, et al. Multislice spiral computed tomography coronary angiography in patients with stable angina pectoris. *J Am Coll Cardiol*. 2004;43:2265–2270.
16. Bae T. Intravenous contrast medium administration and scan timing at CT: considerations and approaches. *Radiology*. 2010;256:32–61.
17. Loewe C, Becker CR, Berletti R, et al. 64-Slice CT angiography of the abdominal aorta and abdominal arteries: comparison of the diagnostic efficacy of iobitridol 350 mgI/mL versus iomeprol 400 mgI/mL in a prospective, randomised, double-blind multi-centre trial. *Eur Radiol*. 2010;20:572–583.
18. Bååth L, Besjakov J, Oksendal A. Sodium-calcium balance in nonionic contrast media. Effects on the risk of ventricular fibrillation in the isolated rabbit heart. *Invest Radiol*. 1993;28:223–227.
19. Jynge P, Holten T, Oksendal AN. Sodium-calcium balance and cardiac function with isotonic iodixanol: an experimental study in the isolated rat heart. *Invest Radiol*. 1993;28:20–25.
20. Jynge P. Sodium-calcium balance in coronary angiography and experimental experience with iodixanol. *Eur Radiol*. 1996;6(suppl 2):S8–S12.
21. Murdock DK, Euler DE, Kozeny G, et al. Ventricular fibrillation during coronary angiography in dogs: the role of calcium-binding additives. *Am J Cardiol*. 1984;54:897–901.
22. Schmid I, Didier D, Pfammatter T, et al. Effects of non-ionic iodinated contrast media on patient heart rate and pressures during intra-cardiac or intra-arterial injection. *Int J Cardiol*. 2007;118:389–396.
23. Manninen H, Tahvanainen K, Borch KW, et al. Iodixanol, a new non-ionic, dimeric contrast medium in cardioangiography: a double-masked, parallel comparison with iopromide. *Eur Radiol*. 1995;5:364–370.
24. Svensson A, Ripsweden J, Rück A, et al. Heart rate variability and heat sensation during CT coronary angiography: low-osmolar versus iso-osmolar contrast media. *Acta Radiol*. 2010;51:722–726.
25. Herzog C, Zwerner PL, Doll JR, et al. Significant coronary artery stenosis: comparison on per-patient and per-vessel or per-segment basis at 64-section CT angiography. *Radiology*. 2007;244:112–120.
26. Rixe J, Rolf A, Conradi G, et al. Detection of relevant coronary artery disease using dual-source computed tomography in a high probability patient series: comparison with invasive angiography. *Circ J*. 2009;73:316–322.
27. Onuma Y, Tanabe K, Chihara R, et al. Evaluation of coronary artery bypass grafts and native coronary arteries using 64-slice multidetector computed tomography. *Am Heart J*. 2007;154:519–516.
28. Grosse C, Globitis S, Hergan K. Forty-slice computed tomography of the coronary arteries: assessment of image quality and diagnostic accuracy in a non-selected patient population. *Acta Radiol*. 2007;48:36–44.