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FULL PAPER

Stent evaluation by coronary computed tomography angiography: a comparison between Iopamidol-370 and Ioversol-320 hypo-osmolar iodine concentration contrasts

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Objective: Qualitative and quantitative image analysis between Iopamidol-370 and Ioversol-320 in stents´ evaluation by coronary computed tomography angiography (CTA).

Methods: Sixty-five patients with low-risk stable angina undergoing stent follow-up with coronary CTA were assigned to Iopamidol I-370 (n = 33) or Ioversol I-320 (n = 32) in this prospective, double-blind, non-inferiority, randomized trial. Stent lumen image quality was graded by 5-point Likert Scale. Lumen mean attenuation was measured at native coronary segments: pre-stent, post-stent, distal segments and at coronary plaques. Lumen attenuation increase (LAI) ratio was calculated for all stents. Heart rate (HR) variation, premature heart beats (PHB), heat sensation (HS), blooming and beam hardening were also assessed.

Results: Image quality was similar between groups, with no significant difference (Likert score 4.48 ± 0.75 *vs* 4.54 ± 0.65, p = 0.5). There were similarities in LAI ratio between I-370 and I-320 (0.39 ± 0.42 *vs* 0.48 ± 0.44 HU, p = 0.08). Regarding lumen mean attenuation at native coronary segments, a significant difference was observed, with I-320 presenting lower values, including contrast mean attenuation in distal segments. After statistical multivariate analysis, three variables correlated with stent image quality: 1) stent diameter, 2) HR variation and 3) stent lumen LAI ratio.

Conclusions: There was no significant difference between Iopamidol-370 mgI ml^{-1} and Ioversol-320 mgI ml^{-1} contrasts regarding overall stent lumen image quality, which was mainly influenced by stent diameter, HR and LAI ratio.

Advances in knowledge:
Coronary CTA allows adequate stents' visualization and image quality is influenced by stent diameter, HR variation and LAI ratio.
Stents' image quality showed no difference between different concentration contrasts (I-370 vs. I-320); however, higher concentration contrasts may provide an improved overall visualization, especially regarding coronary distal segments.

INTRODUCTION

The rate of percutaneous coronary intervention (PCI) in stable coronary artery disease (CAD) has decreased since the introduction of the Appropriateness Criteria for coronary revascularization in 2009[1] and also due to treatment improvements.[2] However, PCI remains as the most frequently used method for revascularization, outnumbering surgery at a ratio around eight-fold. Each year, more than one million patients with CAD are treated with stent implantation.[3]

In those patients, coronary computed tomography angiography (CTA) is considered a reliable non-invasive diagnostic tool for stent evaluation, providing accurate information on stent lumen stenosis.[4] The American Heart Association Guidelines also highlights the role of CTA for the evaluation of stent patency in a variety of clinical settings.[5] Nevertheless, it is important to acknowledge the technical challenges in imaging the stent lumen by CTA. Artifacts generated by the incidence of X-rays over metal structures (blooming and beam hardening) may reduce CTA's diagnostic accuracy, particularly in thick-strut or small diameter stents.

Among many studies that have attempted to address these issues, a recent one has demonstrated that using a

higher-iodine concentration contrast (Iomeprol-400 *vs* Iodixanol-320) negatively affects coronary artery stent evaluation, yielding a worse image quality due to significantly higher beam hardening artifact burden.[6] In daily routine, however, investigating the progression of CAD in untreated coronary segments is crucial, and for achieving optimal images in those territories, iodine concentrations higher than 320 mgI ml^{-1} are recommended.[7] Indeed, the prevalence of higher concentration contrast usage (370 mgI ml^{-1} or above) reaches up to one-third in some large cohorts.[8] Therefore, the current study aims to investigate a non-inferiority performance of contrast Iopamidol-370 mgI ml^{-1} (I-370) compared to Ioversol-320 mgI ml^{-1} (I-320) in the evaluation of coronary artery stents.

METHODS AND MATERIALS

Study design and randomization

This is a prospective, double-blind, non-inferiority, randomized trial which evaluated the enhancing effect of a 370 mgI ml^{-1} concentration contrast media in comparison with a less concentrated agent (320 mgI ml^{-1}) in coronary artery stent evaluation. It is an unicenter study, performed at Sirio-Libanes Hospital, Sao Paulo – Brazil, from August 2015 to October 2016.

Enrolled population included adult patients with prior coronary stents, referred to CTA as part of their clinical care. Eligible patients were randomized in a 1:1 allocation ratio[9] to receive either 370 mgI ml^{-1} (Isovue, Bracco Diagnostic Inc., Singen, Germany) – group I-370, or 320 mgI ml^{-1} (Optiray, Medtronic, São Paulo, Brazil) – group I-320. Exclusion criteria were as follows: prior surgical revascularization, impaired renal function (GFR <60 mL/min/1.73m2), history of hypersensitivity reactions to iodine contrast, pregnancy and contraindications to the use of nitroglycerine. Additionally, as severe obesity is known for degrading image quality in CTA, patients with body mass index (BMI) ≥40 kg/m^2 were excluded as recommended by SCCT Guidelines.[10] The Institutional Ethics Committee approved the study and all participants provided written informed consent.

CTA acquisition protocol

Patients with heart rate (HR) above 65 bpm received up to 100 mg oral and/or 15 mg i.v. metoprolol. All patients received 2.5 mg sublingual nitrate before scanning. An antecubital venous access in the right upper limb (18 gauge) was standard to allow 5 ml s^{-1} intravascular flow for all patients, followed by a 40 ml saline flush. Contrast volume was calculated individually considering the actual weight (1–2 mL/kg).

Scans were performed using a second-generation dual-source CT scanner (SOMATOM Definition Flash, Siemens Healthcare, Forchheim, Germany) with slice configuration of 256×0.6×0.3 mm, gantry rotation of 280 ms, tube potential of 120 kV, an automatic tube current selection algorithm (CAREDose 4D, Siemens Healthcare) and retrospective electrocardiogram gating (65–75% RR).

Data acquisition was performed during a single breath-hold, and the scan ranged from the level of the carina until the diaphragm. A test bolus protocol, with 10–15 ml of contrast, was used to determine optimal contrast arrival timing at the descending aorta. Radiation dose was recorded as effective dose (mSv) and size-specific dose estimate (mGy). Iterative reconstruction was applied using a pre-reconstruction filter for image smoothing and high-frequency noise reduction (Saphyre 2) for both groups, as previously described.[11]

Image evaluation

With the use of axial and multiplanar reconstructions, two experienced physicians (>5 years of experience) performed coronary CTA image evaluation (both qualitative and quantitative) in dedicated workstations (Aquarius versions 4.7–4.11, Terarecon Inc., San Mateo, CA, USA). Disagreements between readers were solved by consensus and used for final analysis. For image interpretation, window width of 1250 and window level of 450 HU were used.[12] Information regarding stent type was unavailable, as their prior implant was performed in multiple sites.

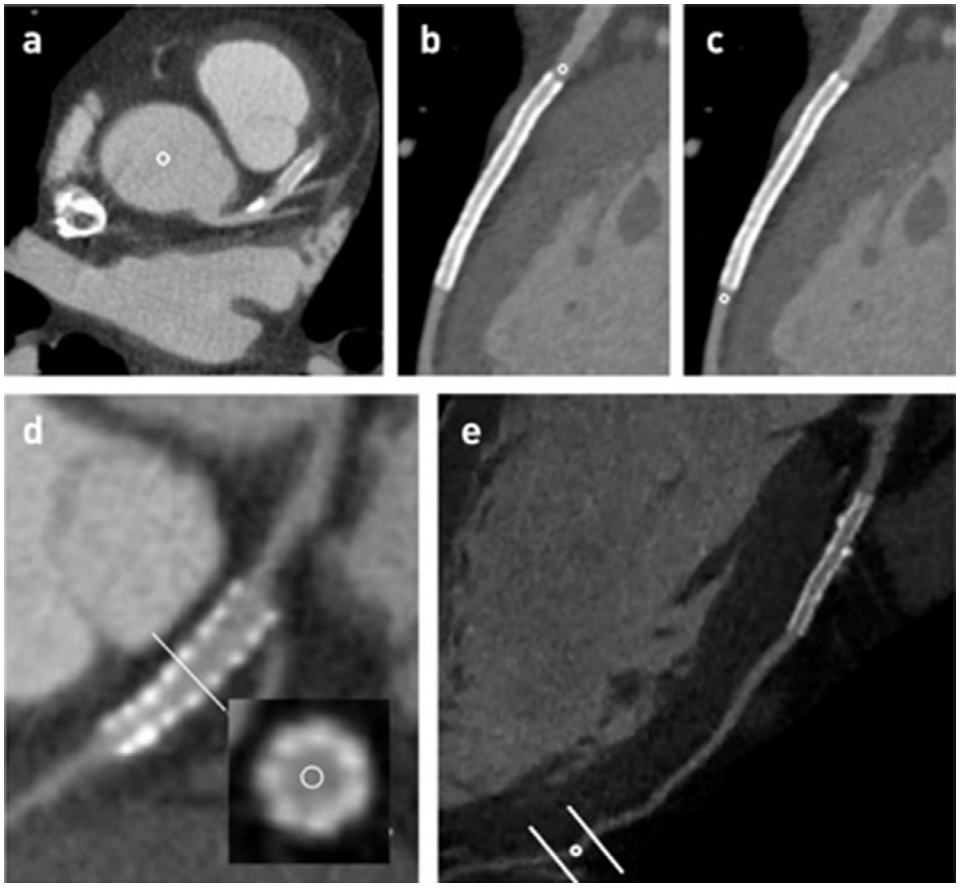
Image quality and quantitative assessment

The primary efficacy measurement was image quality assessed by a 5-point Likert Scale: 5 = excellent (excellent attenuation of the vessel lumen and clear definition of its walls without artifacts), 4 = very good (very good attenuation of the vessel lumen, with defined walls and minimal image noise, without limitation to the diagnosis), 3 = good (slight limitation for vessel lumen attenuation and presence of more detectable noise, but without impairment of the vessel wall definition), 2 = regular (moderate limitation of vessel lumen attenuation and presence of noise that diminish image quality, with mild to moderate impairment of vessel wall definition and final diagnosis), 1 = poor (great limitation of the vessel lumen attenuation, excessive noise and poor definition of the vessel wall, with impossible diagnosis).

Quantitative evaluation was also performed to evaluate image quality. Lumen mean contrast attenuation measurements were performed through manually traced 1.0 mm^2 regions of interest (ROI) at the aortic root, pre-stent coronary segments (defined as 1.0 mm above the stented segment), post-stent coronary segments (defined as 1.0 mm below the stented segment), stented segments, coronary plaques (defined as predominantly calcified with moderate luminal stenosis) and at distal coronary segments (defined as segments with 1.5 to 2.0 mm diameter) (Figure 1). All ROI measurements were performed in the reconstructed transversal plane. To assess high-attenuation stents, in all patients, a correction of the stent lumen mean attenuation was performed according to the pre-stent mean attenuation, as previously described (stent lumen attenuation–pre-stent lumen attenuation/pre-stent lumen attenuation), defined as LAI ratio.[13]

Contrast-to-noise ratio (CNR) and signal-to-noise ratio (SNR) were determined in both groups. The noise was obtained from the standard deviation (SD) of the stent lumen mean attenuation (HU), after ROI measurement. CNR was determined by dividing the mean attenuation difference between the stent lumen and myocardium measurements (obtained by individual ROIs) by the image noise. SNR was calculated by dividing stent lumen mean attenuation by the image noise.

Figure 1. Schematic ROI measurements in the aorta (a), pre-stent (b), post-stent (c), stent lumen (d) and distal coronary segment (e).



Other measurements included the presence of stent blooming artifacts according to a 3-point scale, as previously described,[14] and the presence of beam hardening. Stent lumen restenosis was assessed qualitatively (presence or absence) and confirmed by the corrected coronary opacification (CCO) difference (CCO pre-stent–CCO post-stent; CCO = coronary artery mean attenuation/descending aorta mean attenuation on the same axial section). Finally, the orthogonal wall thickness (OWT = stent external diameter - stent internal diameter / 2) was calculated in all stents, which correlates to the stent's structure thickness and its true diameter after angioplasty, as previously reported.[15]

Study safety

Accordingly, any adverse event reported up to 30 minutes after the examination that had its causal relationship to the iodine contrast media was evaluated. Patient heat discomfort was assessed onsite using the Visual Analog Scale (VAS), a 0–10 point score (zero = no heat and ten = very intense heat).[16]

Statistical analysis

Descriptive data are expressed as mean ± standard deviation and frequency (percentage). To investigate the distribution of continuous variables, graphical evaluations were performed with QQ-plot and confirmed using the Shapiro-Wilk test. Comparisons between I-320 and I-370 groups were made by Student's t-test (or Wilcoxon Rank-sum) and Chi-square (or Fisher's exact) for continuous and categorical variables, respectively.

To investigate which variables (including age, sex, BMI, HR, stent diameter, OWT, tube current, contrast attenuation proximal to stent, LAI ratio, stent lumen SNR and CNR, and allocated protocol group) were associated with better image quality in the Likert scale, an ordinal logistic regression model was used. All variables that presented a level of significance <0.15 in the univariate analysis were included in the adjusted final model. Because multiple stents were examined per patient, a mixed-effects model was used for regression analysis to account for intrapatient correlation. All statistical analyses were performed using R v.3.5.3 (R Foundation for Statistical Computing, Vienna, Austria) and a *P*-value of <0.05 was considered statistically significant.

RESULTS

Baseline characteristics

Sixty-five patients were randomized in the study (33 for group I-370 and 32 for I-320) with a total of 156 stents. Baseline patient and stent characteristics are shown in Tables 1 and 2, respectively. There were no clinical differences between groups. Mean acquisition HR was similar (55 ± 5 bpm for I-370 *vs* 57 ± 6 bpm for I-320, $p = 0.24$). Nearly half of stents were located at

Table 1. Patient baseline characteristics

	I-370 (n = 33)	I-320 (n = 32)	p-value
Demographics			
Age, years	64 ± 8	62 ± 11	0.58
Male, n (%)	30 (91)	26 (81)	0.44
BMI, kg/m^2	28 ± 3	27 ± 4	0.54
Cardiovascular risk factors			
Hypertension, n (%)	18 (55)	20 (63)	0.69
Dyslipidemia, n (%)	11 (33)	15 (47)	0.39
Diabetes, n (%)	9 (27)	7 (22)	0.83
Smoking, n (%)	6 (18)	3 (9)	0.47
FHx-CAD, n (%)	20 (61)	13 (41)	0.17
Acquisition parameters			
HR, bpm	55 ± 5	57 ± 6	0.24
HR <65 bpm	33 (100)	31 (97)	0.98
PHB, n (%)	2 (6)	0 (0)	0.49
Tube voltage, kV	120	120	-
Tube current, mA	404 ± 173	341 ± 67	0.33
VAS for heat sensation	5.7 ± 1.7	4.9 ± 2.1	0.11
Dose-length product, mGy	413.2 ± 133.8	409.9 ± 108.9	0.91

BMI, body mass index; FHX-CAD, family history of early coronary artery disease;HR, heart rate; PHB, premature heartbeats; VAS, visual analog scale; bpm, beats per minute.
Values are given as mean ± SD or absolute numbers and percentages.

left anterior descending coronary artery (LAD) in both groups, being the vast majority ≥3 mm (Table 2). Neither stent size nor OWT were significantly different between groups. Visually, no patient presented stent stenosis, which was confirmed by CCO measurements.

No contrast extravasations occurred and no adverse reactions on the two iodine concentration contrast groups were reported. VAS heat sensation between groups was not different (5.8 ± 1.7 for I-370 *vs* 4.9 ± 2.1 for I-320, p = 0.11).

Image quality

There was no significant difference between groups I-370 and I-320 in the qualitative evaluation (Likert scale: Likert ≥ 4 in 90% for I-370 *vs* 87% for I-320, p = 0.71; and mean 4.5 ± 0.8 *vs* 4.5 ± 0.7, p = 0.5) (Table 2). Only one-third of stents presented mild blooming and 2% presented beam hardening artifacts, with no statistical difference between groups. There were 11 disagreements (<1%) between the two readers, all solved by consensus.

Although I-370 generated significantly higher mean attenuation values in pre-stent than I-320, in most cases of both groups this value was <400 HU (67% *vs* 76%, p = 0.29). Stent lumen SNR and CNR were higher in I-370, given its higher values for stent lumen mean attenuation and lower noise when compared to I-320 (Table 2).

Variables that influenced image quality (univariate analysis) were stent diameter, tube current, HR and LAI ratio. In the multivariate analysis (Table 3), stent diameter, HR and LAI ratio remained significantly associated with image quality. Adjusted effects of these three variables on image quality can be seen in Figure 2.

Native coronary tree contrast enhancement analysis

In coronary plaques, lumen mean attenuation was higher in group I-370 compared to I-320 (414.3 *vs* 351.1, p = 0.002). Group I-370 provided significantly higher lumen mean attenuation in distal segments compared to I-320 (306.9 ± 61.4 *vs* 264.9 ± 69.1, p = 0.01) (Figure 3).

DISCUSSION

For the first time, this study demonstrated the non-inferiority of Iopamidol 370 mgI ml^{-1} in providing evaluable CT scans for assessment of coronary artery stents, as compared to Ioversol 320 mgI ml^{-1}. Both contrasts provided adequate interpretation of stent lumen, with the majority presenting Likert scale 4 to 5. Stent size followed by HR and LAI ratio were the factors associated with image quality. Considering the native coronary tree, I-370 yielded a significantly higher mean attenuation, particularly in distal segments, than I-320.

Table 2. Stent characteristics, quantitative analysis and image quality

	I-370 ($n = 71$)	I-320 ($n = 85$)	p-value
Stent diameter, mm	3.31 ± 0.53	3.34 ± 0.52	0.78
Stent diameter ≥3 mm, n (%)	62 (87)	76 (89)	0.88
OWT, mm	0.63 ± 0.22	0.59 ± 0.23	0.19
Stent location			0.65
LAD, n (%)	36 (51)	38 (44)	
CX, n (%)	17 (24)	20 (24)	
RCA, n (%)	18 (25)	27 (32)	
CCO difference	0.14 ± 0.17	0.17 ± 0.22	0.33
Stent lumen quantitative analysis			
Mean attenuation, HU	523.7 ± 140	508.8 ± 149.5	0.56
Myocardial attenuation, HU	73.5 ± 8	70.6 ± 6.5	**0.014**
Noise, HU	41 ± 18	49.7 ± 20	**0.002**
SNR	16.9 ± 7.9	14.4 ± 10.8	**0.006**
CNR	14.2 ± 6.9	12.3 ± 9.4	**0.006**
LAI ratio	0.39 ± 0.42	0.48 ± 0.44	0.08
Reference vessel			
Aortic root, HU	387.7 ± 53.8	343.2 ± 68.5	**<0.001**
Pre-stent, HU	384.1 ± 63.6	348.1 ± 61.4	**<0.001**
Pre-stent <400, HU	48 (67)	48 (76)	0.29
Post-stent, HU	329.1 ± 90.6	291.3 ± 103.1	**0.001**
Stent lumen image quality			
Likert ≥ 4, n (%)	62 (87)	77 (90)	0.71
Likert	4.5 ± 0.8	4.5 ± 0.7	0.50

CCO, corrected coronary opacification; CNR, contrast-to-noise ratio; CX, left circumflex artery; LAD, left anterior descending coronary artery; LAI, lumen attenuation increase; RCA, right coronary artery; SNR, signal-to-noise ratio.
Values are given as mean ± SD or absolute numbers and percentages.
LAD, CX and RCA branches were attributed to the main artery.

A previous large trial with 234 patients showed that Ioversol-320 provides significantly higher stent evaluability than Iomeprol-400 given the lower number of severe beam hardening artifacts produced by the former.[6] In the current study, the effects of I-370 and I-320 (injected at same flow rate) were similar, with no differences in image quality, number of artifacts or patient safety. As reported by those authors, contrast density in the adjacent coronary segment higher than 400 HU was one of the main predictors of poor stent lumen image quality. This explains in part our results once the pre-stent attenuation was less than 400HU in most cases of both I-370 and I-320 in our study. Indeed, regarding the quantitative assessment of image quality, in accordance with a previous report[17] of improved assessment of stent restenosis,I-370 presented significantly less noise and higher SNR/CNR values than I-320. This difference in noise between contrasts might be due to beam hardening, which influence stent lumen mean attenuation, what may be linked to stents struts.[18]

Furthermore, Cademartiri *et al*[19] observed that higher coronary attenuation significantly improved diagnostic performance in both proximal and distal segments, the greatest benefit was seen in distal segments. In agreement, Christensen et al[20] found that attenuations greater than 300 HU would be more accurate for the evaluation of coronary distal segments. In the present study, the mean attenuation observed in distal segments (<2 mm) with I-320 was noticeably below than the desirable 300 HU to accurately evaluate them. These findings may have clinical implications. Firstly, stented patients are likely to have diffuse CAD, not sparing distal segments. Secondly, many evidences have highlighted the importance of the identification of high-risk plaque features and the extension of the CAD as markers of adverse prognosis. In such clinical scenarios, therefore, the use of low-iodine concentration contrast media may impair an adequate lumen interpretation particularly in distal segments.

Table 3. Variables associated with image quality

Variables	Univariate Ordinal Regression		Multivariate Ordinal Regression	
	Proportional Odds (95% CI)	*p*-value	Proportional Odds (95% CI)	*p*-value
Age, years	1.02 (0.98–1.04)	0.30		
Male	0.51 (0.18–1.30)	0.16		
BMI, kg/m^2*	0.91 (0.82–1.00)	0.06	1.15 (0.62–2.17)	0.34
HR, bpm*	0.51 (0.37–0.69)	<0.001	0.64 (0.43–0.94)	**0.02**
I-370 protocol	0.84 (0.44–1.60)	0.61		
Diameter, mm	7.93 (3.72–18.3)	<0.001	5.39 (2.38–13.2)	**<0.001**
OWT	0.84 (0.44–1.60)	0.81		
Tube current, mA†	0.82 (0.72–0.92)	0.001	0.90 (0.76–1.07)	0.25
Mean attenuation proximal to stent, HU†	1.06 (0.83–1.35)	0.63		
LAI ratio	0.18 (0.08–0.38)	<0.001	0.42 (0.18–0.99)	**0.04**
Stent lumen SNR, HU†	1.81 (0.31–12.4)	0.51		
Stent lumen CNR, HU†	1.39 (0.19–12.3)	0.74		

BMI, body mass index; PHB, premature heartbeats; bpm, beats per minute.
Values are given as absolute numbers and ranges.
Only relevant variables were eligible for the multivariable regression model.
* every 5-unit increase; † every 50-unit increase.

In line with a significant number of studies, the factors associated with poor image quality in this study were stents´ lumen with a smaller diameter, higher HR variability and higher LAI ratio. Indeed, artifacts which arise from metallic stent struts (particularly in stents with a smaller lumen diameter) are likely to influence accuracy. Graaf et al,[21] using 320-slice CTA evaluation in 53 patients with 89 metallic stents in vessels with diameter under 3 mm, demonstrated a reduced specificity of this method in assessing the incidence of stent lumen restenosis. A lower HR variability (<5 bpm during acquisition) also correlates with better image quality.[6,20,22–24] Present reports regarding the prevalence of HR variability among different iodine concentration contrasts are conflicting. Some studies have demonstrated reduced HR variability when using lower concentration iodine contrasts.[6,22,23] However, other studies[20,25] demonstrated no significant difference between contrasts with different iodine concentrations regarding HR variability, what is in accordance with our findings. Finally, LAI ratio is useful to assess high-attenuation stents, which is a measurement mostly related to beam hardening artifacts.[26,27] In fact, the lower LAI ratio, the better the image quality for this location (Figure 3) in quantitative analysis. In the current study, similar values of mean stent lumen attenuation were observed between the two contrasts evaluated (523.7 ± 140 *vs.* 508.8 ± 149.5, $p = 0.56$), which correlates with qualitative image analysis without difference among groups.

The following study limitations are acknowledged. Firstly, there was no information regarding stents' type (technical specifications, polymer composition, diameter and geometrical structure), as most patients do not provide reliable information in clinical practice routine. Therefore, this trial could not account potential differences in stents' type between contrast groups,

Figure 2. Effect plots of the association between stent diameter, LAI ratio and heart rate with image quality. Plot displays the stacked effect for the proportional odds from the multivariable ordinal logistic regression model, showing probabilities across the response categories.

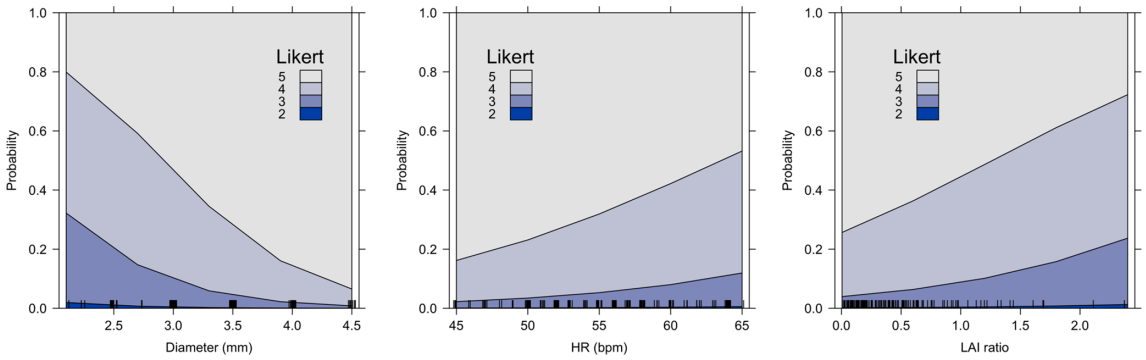
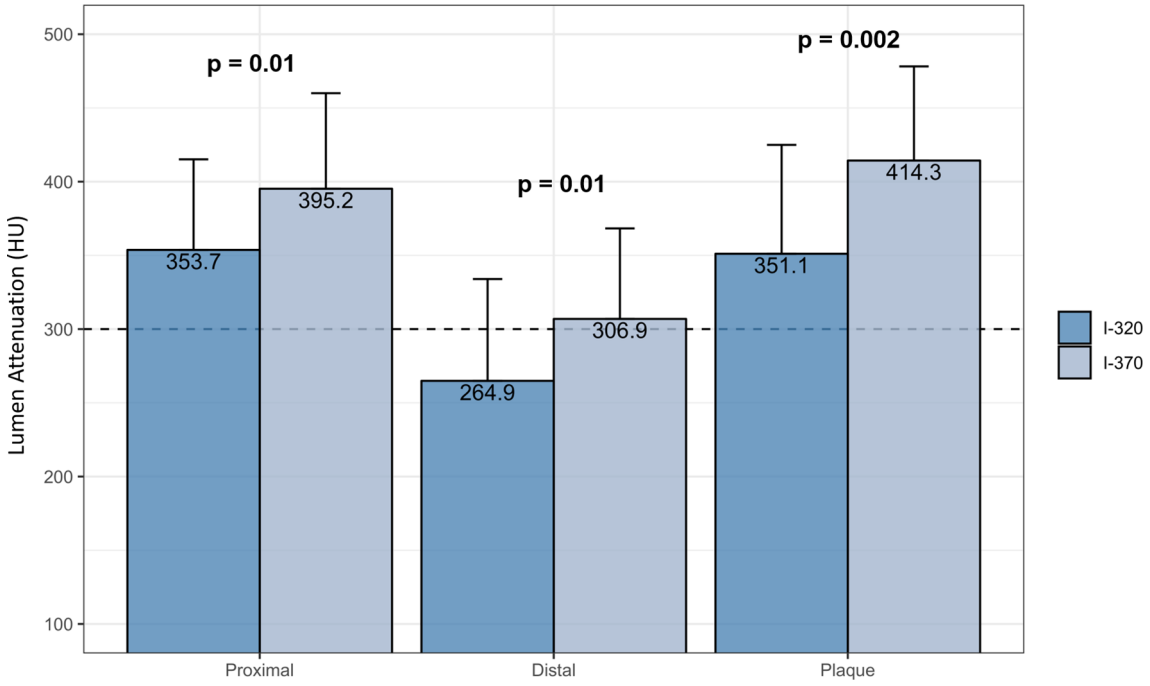


Figure 3. Lumen mean attenuation in coronary plaques, proximal (pre-stent) and distal coronary segments (diameter <2 mm) according to contrast type. Error bars indicate standard deviation of the mean attenuation.



what might have had an additional impact on image quality. However, in the study of Cui et al,[28] true *in vivo* stent diameter relied on vessel shape and dilatation pressure during angioplasty (with possible retraction after placement), not necessarily corresponding to the nominal stent diameter provided by the manufacturer. Considering this, orthogonal stent wall thickness was calculated as in a previous study,[15] whose measure is a reliable surrogate of the true *in vivo* stent wall thickness, and indirectly provides the actual diameter of the placed stent. Secondly, stent lumen restenosis was absent, which is aligned with its low prevalence in the literature.[29,30] At last, a relatively small sample was included. Certainly, future studies with a larger patient population are needed to reinforce data about stent lumen attenuation and image quality.

CONCLUSIONS

There was no significant difference between Iopamidol 370 mgI ml^{-1} and Ioversol 320 mgI ml^{-1} contrasts regarding overall stent lumen image quality, which was mainly influenced by stent diameter, HR and LAI ratio. The contrast with higher iodine concentration may provide a better overall visualization given its effects on native coronary tree, with less noise, especially in distal coronary segments.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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PATIENT CONSENT

The Institutional Ethics Commitee approved the study and all patients provided written informed consent.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This project was clearly described and outlined, with documentation presented in accordance with current legislation and institutional terms. It was registered at CEPesq as HSL 2015–91 and was approved according to the version sent (Stent Project and Free and Informed Consent Term, Version 2.0 of September 2015).

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