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MDCT angiography for detection of pulmonary emboli: Comparison between equi-iodine doses of iomeprol 400 mgI/mL and iodixanol 320 mgI/mL

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Abstract

Objectives: To compare iomeprol 400 and iodixanol 320 in pulmonary artery MDCTA in subjects with suspected pulmonary embolism.
Methods: Eighty randomized subjects received equi-iodine intravenous doses (48 g) of iomeprol 400 ($n = 40$) or iodixanol 320 ($n = 40$), via power injector at 4 mL/s. Four-row (35 subjects) and 64-row (45 subjects) scanners were used. Lumen attenuation was determined on-site and by two off-site blinded readers in the main, lobar, segmental and subsegmental pulmonary arteries. Statistical comparison between groups was performed for demographics and lumen attenuation.
Results: There were no between-group differences ($p > 0.05$) in demographics. Pulmonary artery attenuation was significantly ($p \leq 0.03$) higher with iomeprol 400 for all readers. Attenuation quality was excellent in more patients after iomeprol 400 than after iodixanol-320 (80% vs. 62.5%; 82.5% vs. 77.5%; off-site readers 1 and 2, respectively). No safety concerns were noted.
Conclusion: The greater iodine delivery rate achievable with iomeprol 400 compared to iodixanol-320 at equi-iodine dose and injection rate permits consistently greater attenuation at all levels of the pulmonary arterial tree.

Keywords: Computed tomography (CT), angiography; Computed tomography (CT), contrast enhancement; Contrast media, comparative studies; Pulmonary arteries, CT; Embolism, pulmonary

1. Introduction

Multi-slice computed tomography (MSCT) is now the technique of choice for detection of suspected pulmonary emboli (PE) [1–12]. The possibility to perform MSCT angiography of the entire pulmonary arterial vasculature within a single short breath-hold, and to obtain high spatial resolution with visualization down to the fifth- and sixth-order pulmonary arteries, results in excellent sensitivity and specificity for the detection of PE [2]. The technique is considered sufficiently robust and reproducible to have served as the reference standard in a study to determine the diagnostic accuracy of MR imaging for the diagnosis of PE [13].

To date, many studies have utilized contrast agents (CA) with iodine concentrations ranging between 300 [3–6] and 350 mgI/mL [9,10]. Typically, 100–120 mL of CA are injected at flow rates of 3–5 mL/s, resulting in total iodine doses of 35–36 g and iodine delivery rates ranging between 0.9 and 1.75 gI/s [3–6,9,10]. Recent studies by Schoellnast et al. [11,12] have compared a CA with standard iodine concentration (300 mgI/mL) delivered at 1.2 gI/s with a CA containing high iodine concentration (400 mgI/mL) delivered at 1.6 gI/s (equal total iodine dose of 36 g) for MSCT angiography of the pulmonary arteries, and found that pulmonary arterial enhancement and visualization of subsegmental pulmonary arteries is improved with higher iodine delivery rate. Similar findings have been reported by Setty et al. [14] for a comparison of CA

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containing standard and high iodine concentrations (300 and 370 mgI/mL, respectively) in patients undergoing routine chest MSCT.

Increasing the iodine delivery rate using standard concentration CA can be achieved either by increasing the injection duration or increasing the contrast injection rate. Unfortunately, increasing the injection duration would result in longer bolus lengths and the increased possibility of the scan acquisition being out-run, particularly given the faster gantry rotation times and correspondingly short acquisition times of the most recent 16- and 64-slice CT scanners. On the other hand, increased contrast injection rates may be associated with an increased risk of contrast extravasation, and are not always possible in all patients, particularly in old or frail patients with small or fragile arterial access.

An alternative approach therefore is to use a CA with high iodine concentration. Potential advantages are that the iodine delivery rate can be increased for a given iodine dose without having to alter the contrast injection rate, and that the overall volume of CA administered can be reduced. In addition, the overall time required to administer the full iodine dose can be reduced, thereby maximizing the achievable pulmonary arterial attenuation within the comparatively short acquisition time of the CT scan. Our study was therefore performed to evaluate the impact of iodine delivery rate on pulmonary arterial enhancement after administration of a CA with high iodine concentration (iomeprol 400; Iomeron®-400 mgI/mL; Bracco, Milan, Italy) compared with that achieved after administration of a CA with standard iodine concentration (iodixanol 320; Visipaque™-320 mgI/mL; GE Healthcare, Milwaukee, WI, USA) at equi-iodine dose and injection rate. Unlike previous studies this study was performed on both four-slice and 64-slice CT scanners.

2. Materials and methods

This was a single-center, randomized, double blind, parallel-group comparison study of iomeprol 400 and iodixanol 320 in MSCT angiography (MSCTA) of the pulmonary arteries in 80 patients with suspected pulmonary embolism. The study was approved by the Ethics Review Board of the Medical University of Vienna and the General Hospital Vienna (Ethik-Kommission, Vienna, Austria). All patients gave written informed consent prior to enrollment in the study.

2.1. Patient population

Patients referred for MSCTA of the pulmonary arteries for suspicion of pulmonary emboli who were ≥40 years of age were eligible for enrollment. Patients were ineligible if they had a history of hypersensitivity to iodine-containing compounds; severe congestive heart failure (class III or IV in accordance with the classification of the New York Heart Association); significant renal failure (serum creatinine >2.5 mg/dL) or had undergone any other radiological procedure utilizing X-ray contrast media during the 24-h period preceding the MSCT examination. Patients with hyperthyroidism or thyroid malignancies, uncontrolled diabetes, unstable renal function, drug dependence, psychiatric disorders or dementia were also ineligible, as were subjects who had received an investigational drug within 30 days prior to the study or had any medical condition or other circumstances that would significantly decrease the chances of obtaining reliable data or of completing the study and post-dose follow-up examinations. Finally, nursing or pregnant female patients were also ineligible. The investigator also excluded any subject who he considered to be clinically unsuitable for the study (e.g., patients with systemic arterial hypotension).

2.2. MSCT angiography

MSCT angiography of the pulmonary arteries was performed on either a four-slice (Siemens Somatom Volume Zoom Plus 4; Siemens Medical Systems, Erlangen, Germany) or 64-slice (Siemens Somatom Sensation Cardiac 64; Siemens Medical Systems) CT scanner (gantry rotation times 0.5 and 0.33 s, respectively) in a caudal to cranial direction from the dome of the diaphragm to the aortic arch. Four-slice CT angiography was performed with 4 mm × 1 mm collimation, pitch = 1.75, table feed = 7 mm/rotation, reconstruction slice thickness = 1.25 mm and reconstruction increment = 0.8 mm. Sixty-four-slice CT angiography was performed with 64 mm × 0.6 mm collimation, pitch = 1, table feed = 38.4 mm/rotation, reconstruction slice thickness = 1 mm and reconstruction increment = 0.8 mm. The current and X-ray tube voltage were 120 mA and 120 kV, respectively, for all examinations on both scanners. All scans were performed during breath-hold and the total image acquisition times were 36 and 13 s, respectively.

2.3. Contrast administration

Subjects were randomly assigned to receive either iomeprol 400 or iodixanol 320 at an equi-iodine final dose of 48 gI per subject at a constant rate of 4 mL/s (equating to 120 mL per subject of iomeprol 400 at an iodine delivery rate of 1.6 gI/s for 30 s and 150 mL per subject of iodixanol 320 at an iodine delivery rate of 1.28 gI/s for 37.5 s). CA injections were performed by power injector (Ulrich Ohio Tandem, Ulrich Medical, Ulm, Germany) after pre-warming to 37 °C and were followed by a 40-mL saline flush administered at the same rate. CA assignation and injection was performed according to a dedicated randomization list by an independent drug dispensing person who did not participate in efficacy or safety assessments and whose sole responsibility was to preserve the complete blinding of the investigating radiologist and radiology staff.

The scan delay prior to image acquisition was determined using a semi-automatic bolus-tracking system (Care bolus; Siemens Medical Systems) with a threshold of 100 Hounsfield Units (HU) for all examinations. Regions of interest (ROIs) for bolus tracking were set in the main pulmonary artery.

2.4. Image evaluation

Images were evaluated in fully blinded fashion by the principal on-site investigator and by two off-site independent highly

experienced radiologists (MLS, CSP) in separate reading sessions. All readers were fully blinded to the contrast agent administered, to all clinical and radiological patient information and to the type of scanner used in each examination. Off-site evaluation was performed of digital images on an image review workstation (DICOMed™ Review v. 3.0.6 software; AETMed SpA) set up to permit routine image reviewing functions (window, level, zoom, pan, etc.) as necessary.

Image evaluation on-site was performed at individual ROIs positioned at the level of the main pulmonary arterial bifurcation, in the right and left pulmonary arteries, in the right and left lower lobe arteries, and in the anterior segmental arteries of the upper lobes, the medial segmental artery of the right middle lobe and the posterior basal segmental arteries of the lower lobes. If pulmonary emboli were detected, additional ROIs were positioned in the three largest emboli and in patent lumen of the same vessels immediately proximal to the emboli.

Off-site image evaluation was performed both quantitatively and qualitatively for each patient individually. All image sets were evaluated by both readers. Quantitative evaluation of CT attenuation values (HU) was performed using Analyze® 6.0 software (Mayo Clinic) at predefined ROIs positioned in the lumens of the main pulmonary artery, the lobar artery, a segmental artery (e.g., posterobasal), and two subsegmental arteries (e.g., posterior and mediobasal branches) of the lower lobe of the left lung. If an embolus was identified in the left lower lobe, or if for any other reason (e.g., scarring, emphysema, resection) the left lower lobe arterial anatomy was unevaluable, equivalent arteries of the right lower lobe were selected. Likewise, if emboli were also identified in the right lower lobe, or its arterial anatomy was unevaluable, the reader was to apply the same evaluation process to the right middle lobe; if emboli or unevaluable anatomy were also present there, the reader was to evaluate the lingula in like manner. If all four of these regions were affected by emboli or had unevaluable anatomy, or if the overall quality of enhancement was considered inadequate for the diagnosis of pulmonary emboli, then only the main pulmonary artery was quantitatively evaluated. In each case quantitative analysis was performed on images selected by the blinded readers that best showed the various arterial levels in which vascular attenuation was to be measured. At each arterial level, ROIs of 1–4 mm in diameter were positioned by each reader independently in the centre of the vessel lumen.

Qualitative evaluation was performed for the presence and severity of motion and contrast density (streak) artefacts (1 = none; 2 = not significantly impeding the diagnosis of PE; 3 = impeding the diagnosis of PE), and for the overall quality of attenuation (excellent, fair, or inadequate). All qualitative evaluations were independently and subjectively made by the off-site blinded readers.

2.5. Statistical analysis

Patient enrollment for this prospective study was based on a sample size calculation by which 39 patients in each group would give 80% power to detect a difference in means of 45 HU (the difference between a group A mean, μ_1, of 325 HU and a group B mean, μ_2, of 280 HU), assuming a common standard deviation of 70 HU using a two group t-test with a two-sided significance level of 0.05. Patients were randomly assigned to receive either iomeprol 400 (group A) or iodixanol 320 (group B). Demographic and baseline characteristics were summarized and compared between CA groups using descriptive statistics (N, mean, S.D., minimum and maximum) or frequency distributions. Differences between the two treatment groups were evaluated using Fisher's test for sex and age group and unpaired t-test for age, weight and height.

Prior to inter-group comparison of contrast attenuation, the quality of the CT attenuation data was confirmed using the Bland and Altman graphical procedure in terms of the average enhancement across the main and segmental pulmonary arteries and the specific enhancement at individual arterial levels. The Shapiro-Wilk W test was used to determine whether the attenuation data followed a normal distribution; the findings from this analysis (W statistic >0.9 in all cases) indicated an approximately normal distribution for determinations by both off-site readers at all evaluated arterial segments, therefore, subsequent testing for between-group differences in CT attenuation at the different levels of the pulmonary arteries was performed using t-tests for unpaired data with 95% confidence intervals. Differences were considered significant for $p < 0.05$. Attenuation quality and assessments of motion and contrast artefacts were presented by frequency and percentage. All statistical analysis was performed using SAS version 8.2 (SAS Institute, Cary, NC) software.

3. Results

A total of 80 subjects were enrolled and randomly assigned to either group A or group B. All patients successfully underwent MSCT angiography; 35 subjects (18 in group A, 17 in group B) underwent MSCT angiography on a four-slice CT scanner, whereas the remaining 45 subjects (22 in group A, 23 in group B) underwent MSCT angiography on a 64-slice CT scanner. No significant differences were apparent between treatment groups in any demographic parameter (Table 1) and no differences in demographics were apparent between patients undergoing four-slice CT angiography compared to 64-slice CT angiography.

3.1. On-site evaluation

The results of the on-site evaluation of images in terms of vessel attenuation are summarized in Table 2. Significantly higher attenuation was achieved with iomeprol 400 in the main pulmonary artery ($p = 0.003$) and at all segmental and subsegmental pulmonary arterial levels examined ($p \leq 0.0074$). The difference in mean attenuation obtained with iomeprol 400 compared to iodixanol 320 increased from 70.3 HU (+21.8%) in the main pulmonary artery to 87.9 HU (+26.1%) in the posterior basal segmental arteries of the right/left lower lobes, and 89.9 HU (+26.9%) in the medial segmental artery of the right middle lobe.

On-site evaluation revealed a total of 14 emboli in group A and 16 emboli in group B. The mean attenuation of the 14 emboli in group A was 59.4 ± 24.8 HU (range: 27–107 HU)

Table 1
Patient demographics

Demographic	Iomeprol 400 ($n=40$)	Iodixanol 320 ($n=40$)	p-Value
Sex, n(%); male/female	18 (45.0)/22 (55.0)	23 (57.5)/17 (42.5)	0.3711[a]
Age (years); mean ± S.D. (range)	69.7 ± 12.6 (49–91)	65.1 ± 11.4 (40–85)	0.0895[b]
Age group, n(%); 18–64 years/≥65 years	15 (37.5)/25 (62.5)	17 (42.5)/23 (57.5)	0.8197[a]
Weight (kg); mean ± S.D. (range)	77.1 ± 19.2 (48–134)	81.9 ± 16.3 (58–120)	0.2399[b]
Height (cm); mean ± S.D. (range)	167.9 ± 8.3 (150–182)	170.8 ± 10.1 (150–191)	0.1763[b]

[a] Fisher's test.
[b] Unpaired t-test.

while that for the 16 emboli in group B was 38.1 ± 23.6 HU (range: 5–88 HU). The difference (21.3 HU; 95% CI: 3.2–39.4) was statistically significant ($p=0.0234$) (Fig. 1). Conversely, the mean attenuation in the patent arteries immediately proximal to the emboli was 380.2 ± 141.1 HU (range: 237–652 HU) for group A and 334.6 ± 50.0 HU (range: 238–396 HU) for group B. Although greater attenuation was achieved with iomeprol 400, the difference (45.6 HU, 95% CI: −31.5 to 122.7) was not significant ($p=0.2681$).

The difference in attenuation between emboli and patent vessel proximal to the emboli was 320.8 ± 122.7 HU (range: 183–545 HU) for group A and 296.5 ± 46.2 HU (range: 219–359 HU) for group B. Again the difference in mean attenuation (24.3 HU; 95% CI: −43.3 to 91.9) was not significant ($p=0.4947$).

3.2. Off-site evaluation

The findings of the two-blinded off-site readers in terms of quantitative vessel attenuation are reported in Table 3. Similar findings to those of the on-site evaluation were found by both readers at all pulmonary artery levels examined. In each case, the attenuation achieved with iomeprol 400 was significantly ($p \leq 0.031$) higher than that achieved with iodixanol 320, with the difference in mean values ranging from 58.8 HU (+18.7%) and 48.8 HU (+14.8%) (readers 1 and 2, respectively) in the main pulmonary artery to 99.3 HU (+25.4%) and 79.3 HU (+20.8%) (readers 1 and 2, respectively) in the sub-segmental arteries.

Off-site blinded evaluation revealed no differences in terms of qualitative attenuation ($p>0.05$; Chi square test). Readers 1 and 2 considered 32/40 (80%) and 33/40 (82.5%) image sets after iomeprol 400 to be of excellent overall quality, respectively, compared with 25/40 (62.5%) and 31/40 (77.5%) image sets after iodixanol 320, respectively. The remaining image sets were all considered to be of fair overall quality, apart from one image set in group A that was considered inadequate by reader 1 because of motion artefacts.

Among the image sets considered to be of fair or excellent image quality, reader 1 noted minor motion artefacts in 9 (22.5%) image sets after iomeprol 400 and in 13 (32.5%) image sets after iodixanol 320. Conversely, reader 2 noted minor motion artefacts in 25 (62.5%) image sets after iomeprol 400 and in 20 (50.0%) image sets after iodixanol 320. Despite some variation between readers, no overall differences between groups A and B were found concerning motion and contrast density (streak) artefacts. No major contrast artefact, which would significantly impede the diagnosis of pulmonary emboli, was found by either reader for either CA.

No major difference in mean attenuation or artefact type or frequency was noted by either off-site blinded reader for image sets acquired on four-slice CT compared to 64-slice CT (Table 4). Higher attenuation at all pulmonary arterial levels was achieved with iomeprol 400 regardless of the scanner used (Figs. 2 and 3). The differences in mean attenuation in the main pulmonary artery for iomeprol 400 compared to iodixanol 320 for four-slice CT angiography were 73.4 HU (+21.9%; 95% CI: 5.8, 141.1 HU) for reader 1 and 57.2 HU (+16.3%; 95% CI: −12.7; 127.1 HU) for reader 2. The corresponding differences for 64-slice CT angiography were 45.2 HU (+15.1%; 95% CI: −6.8, 97.2 HU) for reader 1 and 40.1 HU (+12.8%; 95% CI: −16.5, 96.8 HU) for reader 2. Similarly, higher attenuation with iomeprol 400 was achieved at all other pulmonary arterial levels, with a tendency for a greater difference in attenuation at the level of the segmental and sub-segmental arteries, particularly for reader 1.

Table 2
Quantitative on-site evaluation of MSCT angiography

Arterial segment	Iomeprol 400	Iodixanol 320	Difference[a] (95% CI) [%]	p-Value[b]
Main pulmonary artery	392.3 ± 108.1 ($n=40$)	322.0 ± 97.0 ($n=40$)	70.3 (24.6, 116.0) [21.8]	0.003
Right/left pulmonary arteries	373.4 ± 98.9 ($n=36$)	301.9 ± 87.2 ($n=38$)	71.5 (28.3, 114.6) [23.7]	0.0016
Right/left lower lobe artery	392.9 ± 113.6 ($n=37$)	313.6 ± 89.2 ($n=37$)	79.3 (31.9, 126.6) [25.3]	0.0014
Right/left upper lobe: anterior segmental arteries	402.3 ± 118.0 ($n=37$)	330.6 ± 104.1 ($n=36$)	71.7 (19.8, 123.7) [21.7]	0.0074
Right middle lobe: medial segmental artery	424.3 ± 138.0 ($n=37$)	334.3 ± 95.9 ($n=36$)	89.9 (34.3, 145.5) [26.9]	0.0019
Right/left lower lobe: posterior basal segmental arteries	425.1 ± 135.4 ($n=35$)	337.2 ± 99.2 ($n=33$)	87.9 (30.1, 145.6) [26.1]	0.0032

n = no. of subjects for each vessel segment. Values represent attenuation values in Hounsfield units, mean ± S.D. of right and left segments.
[a] Difference between means for iomeprol 400–iodixanol 320.
[b] Unpaired t-test.

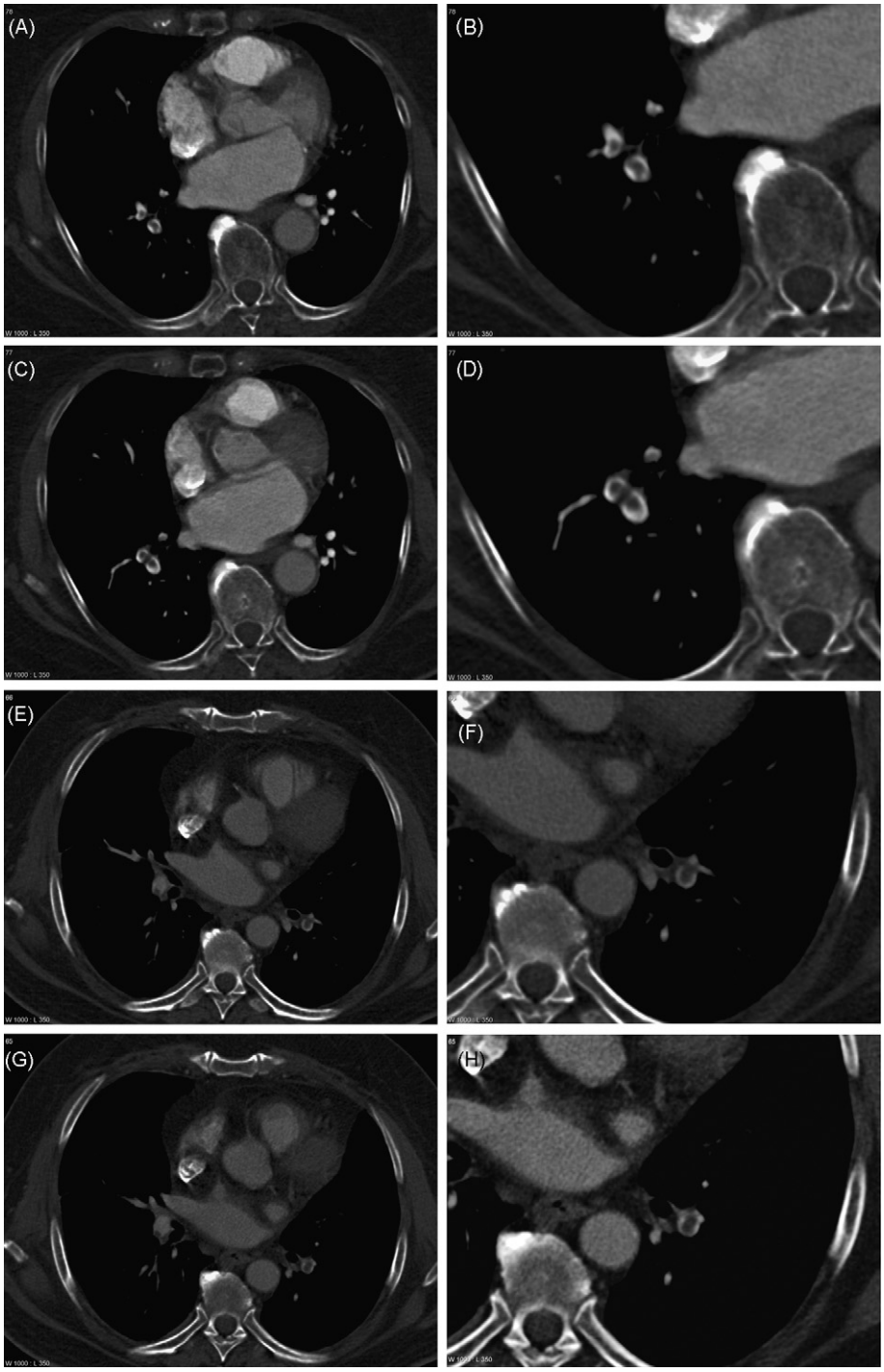

Fig. 1. Comparison of iomeprol 400 (A–D) and iodixanol 320 (E–H) for visualization of pulmonary embolus at CTA (windowing: W 1000/L 350). Image sets of positive pulmonary embolus in two consecutive slices with pulmonary vessel contrast densities closest to the average density values obtained in this study are demonstrated. Images B, D, F and H are magnifications of images A, C, E and G, respectively to better demonstrate the greater contrast attenuation achieved with iomeprol 400 (B and D) compared with iodixanol 320 (F and H).

4. Discussion

Several studies have shown that adequate depiction of the pulmonary arterial vasculature down to the level of the fourth-, fifth- and even sixth-order vessels depends on both a satisfactorily thin collimation [15–20] and on sufficient attenuation in the vessels of interest [11,12,14,21,22]. Higher vessel attenuation can be achieved by increasing the iodine delivery rate, either by increasing the injection flow rate, or by increasing the iodine concentration of the CA used for the study [23]. In the present study, attaining a similar iodine delivery rate of 1.6 gI/s with iodixanol 320 to that achieved with iomeprol 400 for an equivalent total iodine dose and injection duration would have required an increased injection flow rate of 5 mL/s. Unfortu-

Table 3
Quantitative off-site evaluation of MSCT angiography

Arterial segment	Reader	Iomeprol 400	Iodixanol 320	Difference[a] (95% CI) [%]	*p*-Value[b]
Main pulmonary artery	1	373.7 ± 97.2	314.9 ± 91.7	58.8 (16.8, 100.9) [18.7]	0.0067
	2	378.0 ± 100.1	329.2 ± 98.5	48.8 (4.6, 93.0) [14.8]	0.031
Lobar artery	1	403.9 ± 123.4	323.9 ± 88.6	80.0 (31.9, 128.0) [24.7]	0.0015
	2	396.6 ± 118.3	328.5 ± 92.3	68.1 (20.9, 115.3) [20.7]	0.0053
Segmental artery	1	458.1 ± 156.9	359.6 ± 104.0	98.5 (39.0, 158.0) [27.4]	0.0017
	2	435.0 ± 131.6	360.4 ± 107.1	74.5 (21.1, 127.9) [20.7]	0.0069
Sub-segmental artery[c]	1	489.8 ± 173.2	390.6 ± 109.2	99.3 (34.5, 163.9) [25.4]	0.0035
	2	459.9 ± 146.7	380.7 ± 103.2	79.3 (22.8, 135.7) [20.8]	0.0067

Values represent attenuation values in Hounsfield units, mean ± S.D.
[a] Difference between means for iomeprol 400–iodixanol 320.
[b] Unpaired *t*-test.
[c] Higher value between the two sub-segments measured.

nately, increasing the injection flow rate to 5 mL/s and beyond requires the use of IV catheters of larger diameter, which may be impractical in some patients. Thus the most practical approach to increasing the iodine delivery rate in order to improve the visibility of lower order pulmonary vessels is to increase the iodine concentration of the CA.

Studies to compare CA with standard (300–350 mgI/mL) and high (370–400 mgI/mL) concentrations of iodine at equi-iodine dose for MSCT angiography of the pulmonary arteries have consistently demonstrated improved visualization with high concentration CA [11,12,14]. Specifically, studies by Schoellnast et al. [11,12] to compare equi-iodine doses of iomeprol 400 and iopromide 300 for MSCT angiography of the pulmonary arteries not only demonstrated significantly ($p < 0.001$) greater mean pulmonary artery attenuation with iomeprol 400 [11,12], but also significantly ($p < 0.001$) better detection of sixth-order vessels with the higher concentration CA [11]. The total iodine dose for both CA in these studies was 36 gI injected at 4 mL/s for overall iodine delivery rates of 1.6 and 1.2 gI/s for iomeprol 400 and iopromide 300, respectively. Another recent study by Setty et al. [14] similarly revealed significantly ($p < 0.001$) better mean attenuation of the main pulmonary artery with high concentration iopamidol 370 compared to iopamidol 300, when these CA were randomly administered at an equi-iodine dose of 0.4 gI/kg to patients undergoing routine 16-slice chest CT. On the other hand, a recent study by Goodman et al. [24] reported significantly ($p \leq 0.004$) greater attenuation of the pulmonary arteries with iohexol 300 (300 mgI/mL) compared to iodixanol 320 when both CA were administered at 4 mL/s at an equi-iodine dose of 42 gI at iodine delivery rates of 1.2 and 1.28 gI/s, respectively. However, these findings may have been due to the fact that while iodixanol 320 was administered with a 50-mL saline flush, iohexol 300 was administered without any flush. The authors themselves suggest that whereas the saline flush might have been expected to deliver more iodixanol to the pulmonary arteries resulting in greater attenuation, the diminished attenuation actually observed might have been due to dilution of the iodixanol by the saline [24].

As in the studies by Schoellnast et al. [11,12] and Setty et al. [14] the two CA in our study were administered using an identical protocol in which CA administration was followed by a 40-mL saline flush. Our results confirm the findings of these previous studies [11,12,14] in showing that significantly higher attenuation of the pulmonary arterial vasculature down to the segmental and sub-segmental vessels is achievable with

Table 4
Quantitative off-site comparison of four-slice and 64-slice CT angiography

Arterial segment	Reader	Four-slice CT angiography			64-slice CT angiography		
		Iomeprol 400 ($n = 18$)	Iodixanol 320 ($n = 17$)	Difference in means [%]	Iomeprol 400 ($n = 22$)	Iodixanol 320 ($n = 23$)	Difference in means [%]
Main pulmonary artery	1	409.7 ± 92.3	336.2 ± 104.4	73.4 [21.9]	344.2 ± 92.9	299.0 ± 79.7	45.2 [15.1]
	2	409.2 ± 98.7	352.0 ± 104.6	57.2 [16.3]	352.5 ± 96.0	312.4 ± 92.5	40.1 [12.8]
Lobar artery	1	456.6 ± 123.6	355.5 ± 92.2	101.1 [28.4]	363.1 ± 109.3	300.6 ± 80.0	62.6 [20.8]
	2	445.2 ± 123.8	360.5 ± 97.2	84.7 [23.5]	356.9 ± 99.5	304.9 ± 82.7	52.0 [17.1]
Segmental artery	1	507.1 ± 153.2	379.2 ± 114.1	127.9 [33.7]	420.2 ± 152.4	345.1 ± 96.0	75.1 [21.8]
	2	476.1 ± 120.2	382.3 ± 111.7	93.8 [24.5]	401.3 ± 133.6	344.3 ± 103.1	57.1 [16.6]
Sub-segmental artery	1	548.0 ± 195.9	412.0 ± 118.2	136.0 [33.0]	444.9 ± 142.1	374.8 ± 101.9	70.1 [18.7]
	2	510.7 ± 164.1	395.2 ± 98.6	115.5 [29.2]	418.4 ± 118.9	369.9 ± 107.3	48.5 [13.1]

Values represent attenuation values in Hounsfield units, mean ± S.D.

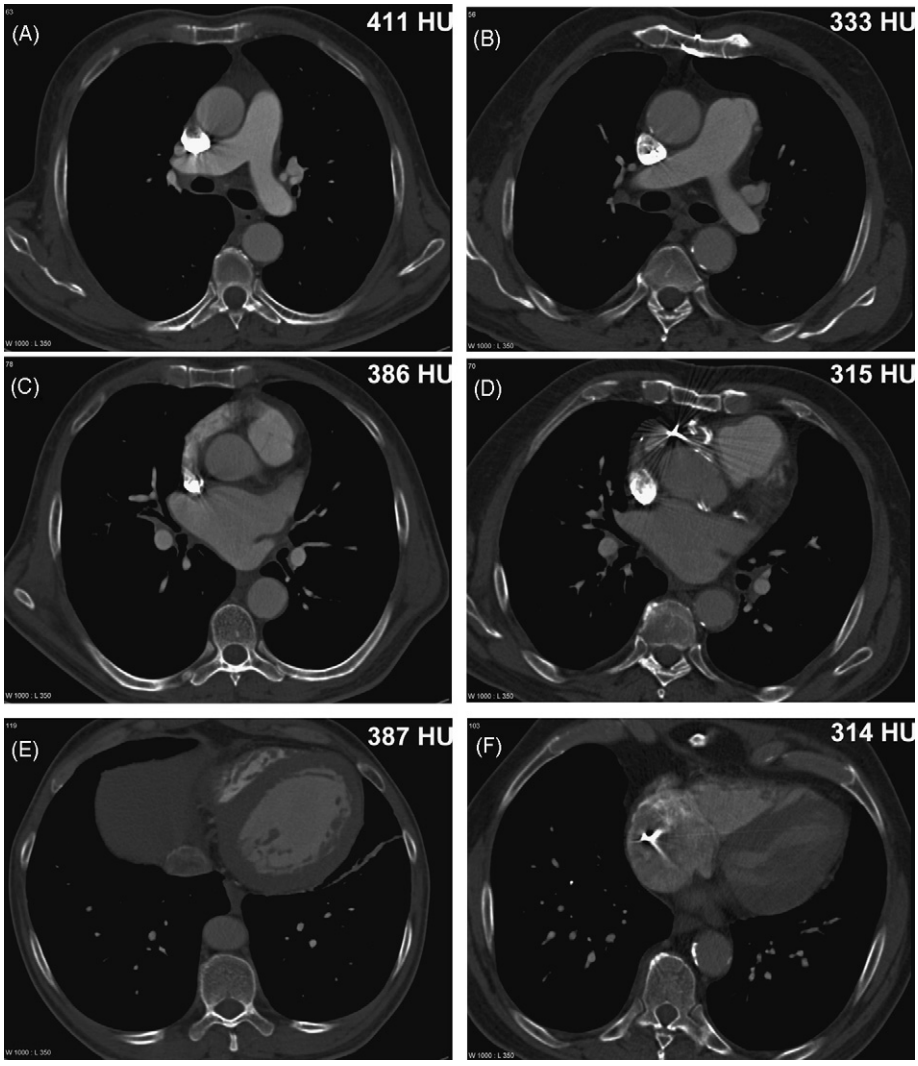

Fig. 2. CTA of the main pulmonary artery and right/left pulmonary arteries (A and B), lower lobe arteries (C and D), and segmental/subsegmental pulmonary branches (E and F) acquired on a four-slice CT scanner (CTA windowing: W 1000/L 350) after iomeprol 400 (A, C, E; left column) and iodixanol 320 (B, D, F; right column). Consistently greater contrast density was achieved with iomeprol 400 compared to iodixanol 320 in each vessel. Image sets with contrast densities closest to the average density values are demonstrated (411 vs. 333 HU for the main pulmonary artery, 386 vs. 315 HU for the left pulmonary artery, and 387 vs. 314 HU for the left lower lobe artery).

high concentration iomeprol 400 compared to standard concentration iodixanol 320, when these CA are administered at an equi-iodine dose of 48 gI at iodine delivery rates of 1.6 and 1.28 gI/s, respectively. Of interest is that the attenuation achieved with iomeprol 400 across the pulmonary arterial vasculature as a whole was roughly 25% higher for all readers than that achieved with iodixanol 320 under identical injection conditions. This increased attenuation corresponds extremely well with the 25% increase in iodine delivery rate achieved with the high concentration CA, further implying that the two patient groups were comparable in terms of heart rate function and other physiological parameters. To note also is that while significantly higher attenuation was obtained at all arterial levels with iomeprol 400 compared to iodixanol 320, both on-site investigators and off-site blinded readers observed that the greatest difference in mean attenuation was at the level of the segmental and sub-segmental vessels. Although specific qualitative assessment of lower order pulmonary vessel visualization was not performed in this study, it is likely that improved visualization of lower order vessels would correlate with improved detection of small PE in these distal vessels. As reported elsewhere [11], the higher concentration iomeprol 400 was not associated with increased artefact presence or reduced image quality when compared with iodixanol 320.

Whereas iomeprol is a nonionic monomeric contrast medium with a low osmolality of 726 mOsmol/kg bodyweight, iodixanol is a nonionic dimeric contrast medium with an osmolality similar to that of human plasma (290 mOsmol/kg bodyweight). Because of its iso-osmolar nature, iodixanol theoretically may be expected to suffer less than iomeprol from plasma dilution after injection [25]. Our results, however, suggest that any potential benefit attributable to this effect was insufficient to outweigh the more rapid iodine delivery rate achieved

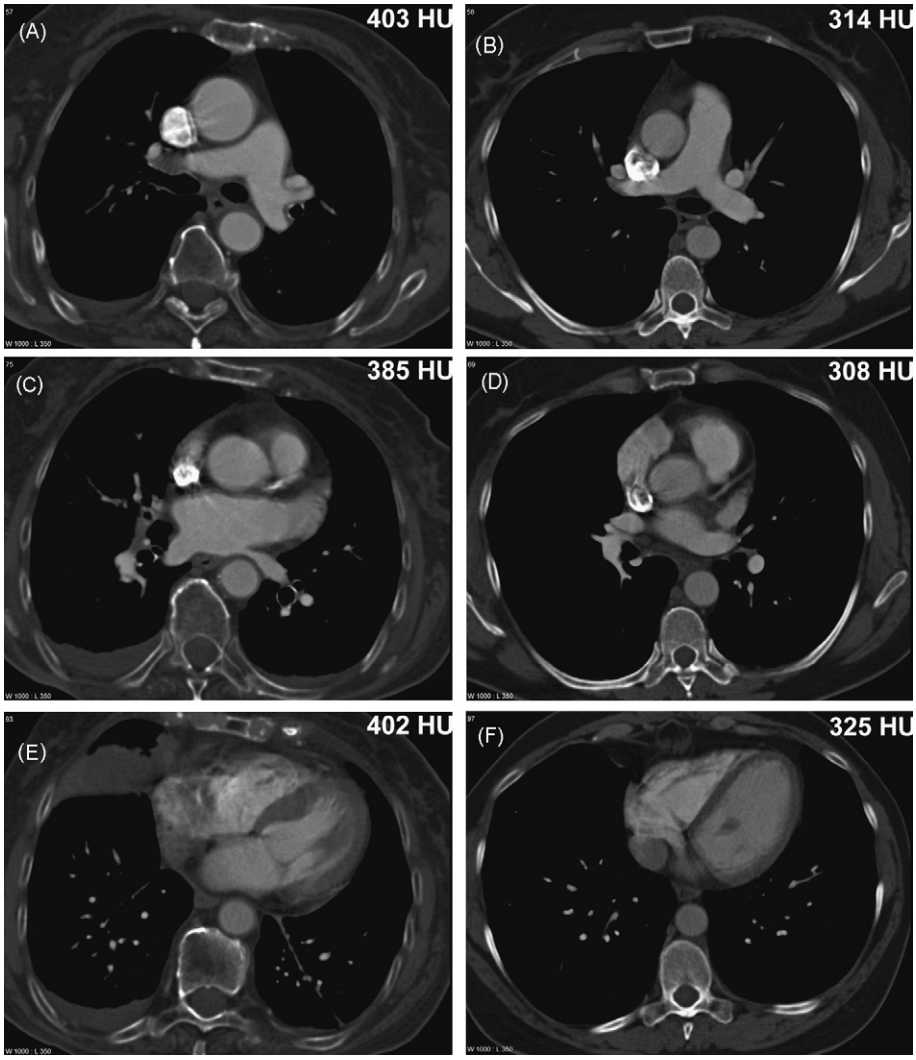

Fig. 3. CTA of the main pulmonary artery and right/left pulmonary arteries (A and B), lower lobe arteries (C and D), and segmental/subsegmental pulmonary branches (E and F) acquired on a 64-slice CT scanner (CTA windowing: W 1000/L 350) after iomeprol 400 (A, C, E; left column) and iodixanol 320 (B, D, E; right column). Consistently greater contrast density was achieved with iomeprol 400 compared to iodixanol 320 in each vessel. Image sets with contrast densities closest to the average density values are demonstrated (403 vs. 314 HU for the main pulmonary artery, 385 vs. 308 HU for the left pulmonary artery, and 402 vs. 325 HU for the left lower lobe artery).

with iomeprol 400. A previous study to determine whether CA osmolarity affects pulmonary artery attenuation in patients with suspected PE similarly revealed that iso-osmolar iodixanol 270 is not associated with any improvement in image quality when compared to the low osmolar CA iohexol 240 [26].

The studies by Schoellnast et al. [11,12] to compare iomeprol 400 with iopromide 300 for pulmonary MSCT angiography were performed exclusively on a four-slice CT scanner. However, with the faster gantry rotation times and correspondingly rapid scan times of the latest 64-slice scanners, there is an increased risk of the CA injection over-running the acquisition time of the scanner. The use of high concentration CA combined with rapid injection (resulting in increased iodine delivery rate) may prove advantageous in this setting in enabling the overall volume of CA to be reduced, thereby maximizing the achievable contrast attenuation during the scan acquisition.

Our results confirm that greater vessel attenuation is achieved with iomeprol 400 compared to iodixanol 320 regardless of whether a four-slice or a 64-slice CT scanner is used; in both cases the greatest benefit was noted at the level of the segmental and sub-segmental arteries. However, a limitation of this study is that the CA administration protocol was optimized for four-slice CT angiography rather than for 64-slice CT angiography. Consequently the greatest attenuation obtained with iomeprol 400, and the greatest difference in attenuation between that obtained with iomeprol 400 and that obtained with iodixanol 320, was observed for the four-slice CT scanner. On the one hand the greater attenuation seen with the four-slice scanner relative to the 64-slice scanner reflects the longer acquisition time of the former and the fact that all or most of the administered dose will have been present in the pulmonary arteries during image acquisition. Conversely, the reduced overall attenuation seen for 64-slice CT angiography possibly reflects the shorter

image acquisition time of the 64-slice CT scanner relative to the contrast injection times and thus the possibility of the contrast bolus out-running the acquisition time. However, it should be borne in mind that synchronization of contrast bolus with the short acquisition times of the latest generation CT scanners is a frequent problem in routine practice and that out-running of the scan acquisition is a comparatively common occurrence, particularly if contrast media with standard concentrations of iodine (300–320 mgI/mL) are used in relatively large volumes. From this point of view our findings for 64-slice CT angiography not only reflect a frequent clinical scenario but also highlight the added value of contrast media with higher concentrations of iodine (370–400 mgI/mL) in that smaller overall volumes can be administered permitting greater contrast medium presence in the vessels of interest during the short scan acquisition time. It is also worth pointing out that out-running of the image acquisition time may not necessarily be a disadvantage if pulmonary MSCT angiography is subsequently combined with MSCT phlebography of the lower extremity veins for the detection of deep venous thrombosis. Although our study reveals benefits for iomeprol 400 compared to iodixanol 320 for four-slice and 64-slice CT angiography alike, further work is certainly needed to optimize the CA injection protocol for pulmonary 64-slice CT angiography.

A second limitation of this study beyond the methodological heterogeneity caused by the use of both four-slice and 64-slice scanners, was the comparatively small number of patients evaluated. Although the 80 enrolled patients were sufficient to demonstrate significantly higher vessel attenuation with iomeprol 400, a larger prospective study involving a greater number of patients with suspected PE may be worthwhile in order to demonstrate a significant clinical impact of the greater vessel attenuation achievable with higher iodine concentration.

In conclusion, our findings show that CT attenuation of the pulmonary arterial vasculature is significantly higher with the use of high concentration iomeprol 400 compared with iodixanol 320 when administered at identical iodine dose and injection rate. The improved attenuation can be directly and proportionately ascribed to a greater iodine delivery rate (1.6 g/s vs. 1.28 g/s). No extra attenuation capability beyond that expected from concentration and iodine delivery rate was noted, and no advantage for one agent over the other was apparent in terms of image quality or streak artefacts. The possibility to increase the iodine delivery rate with high concentration iomeprol 400 without having to increase the contrast injection rate may be a practical solution for patients for whom fast injection rates and/or large IV catheters are impractical, and may prove beneficial for the improved visualization of smaller segmental and subsegmental vessels.

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