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Persistent renal enhancement after intra-arterial versus intravenous iodixanol administration

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Abstract

Purpose—To examine the clinical significance of persistent renal enhancement after iodixanol administration.

Methods—We retrospectively studied 166 consecutive patients who underwent non-enhanced abdominopelvic CT within 7 days after receiving intra-arterial (n=99) or intravenous (n=67) iodixanol. Renal attenuation was measured for each non-enhanced CT scan. Persistent renal enhancement was defined as CT attenuation > 55 Hounsfield units (HU). Contrast-induced nephropathy (CIN) was defined as a rise in serum creatinine $\geq 0.5\text{mg/dL}$ within 5 days after contrast administration.

Results—While the intensity and frequency of persistent renal enhancement was higher after intra-arterial (mean CT attenuation of 73.7HU, seen in 54 of 99 patients, or 55%) than intravenous contrast material administration (51.8HU, seen in 21 of 67, or 31% $p < 0.005$), a multivariate regression model showed that the independent predictors of persistent renal enhancement were a shorter time interval until the subsequent non-enhanced CT ($p < 0.001$); higher contrast dose ($p < 0.001$); higher baseline serum creatinine ($p < 0.01$); and older age ($p < 0.05$). The route of contrast administration was not a predictor of persistent renal enhancement in this model. Contrast-induced nephropathy was noted in 9 patients who received intra-arterial (9%) versus 3 who received intravenous iodixanol (4%), and was more common in patients with persistent renal enhancement ($p < 0.01$).

Conclusion—Persistent renal enhancement at follow-up non-contrast CT suggests a greater risk for contrast-induced nephropathy, but the increased frequency of striking renal enhancement in patients who received intra-arterial rather than intravenous contrast material also reflects the larger doses of contrast and shorter time to subsequent follow-up CT scanning for such patients.

Keywords

CT; intravenous; intra-arterial; contrast; renal; persistent enhancement; contrast-induced nephropathy

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Introduction

The use of intravascular contrast material has steadily risen over the past decades such that current annual usage exceeds 80 million doses (1). Despite the large clinical doses, these agents have been shown to be remarkably safe for the vast majority of patients. Several adverse effects of iodinated contrast material are well known, including allergic-type reactions, extravasations, and renal toxicity, also known as contrast-induced nephropathy (CIN). Renal toxicity has been the subject of ongoing active investigation, and controversy has been raised regarding a possible difference in the mechanism of renal injury when contrast is given intravenously as for computed tomography (CT) as opposed to via an intra-arterial route as for catheter angiography. Catheter angiography may involve procedural risks that could potentially contribute to renal injury, including the mechanical catheterization of the aorta proximal to the renal arteries, sedative drugs that may decrease blood pressure, exposure of end-organs to sudden boluses of relatively concentrated contrast material, and the absence of the filtration effect for particles that is provided by contrast material passage through the pulmonary capillary bed. Unfortunately, few studies have assessed the difference in renal toxicity when contrast material is injected via the vein versus the artery. One review showed that 98.7% of published studies on CIN focused on intra-arterial contrast material injections (2).

Abnormalities on contrast-enhanced nephrograms are known to reflect the presence of underlying urinary tract dysfunction (3–5), but the clinical significance of a delayed CT nephrogram as it relates to prior intra-arterial versus intravenous contrast administration has not been well studied. At routine CT readout of “non-enhanced” scans, we encountered occasional patients with striking prolonged renal enhancement that were found hours, and even days, after prior intravascular contrast exposure. Upon investigation, we found the literature to be conflicting regarding the significance of such findings. While prior studies with non-iodixanol iodinated contrast material showed a higher risk of contrast-induced nephropathy in patients with persistent renal enhancement (6–8), small-scale trials using iodixanol indicated a lack of such correlation in healthy subjects and in non-diabetic patients with chronic renal failure (9, 10). Therefore, the purpose of our study was to examine the appearance and clinical significance of finding persistent renal enhancement after the administration of iodixanol, with a focus on the route of contrast administration and the possible association with contrast-induced nephropathy.

Patients and Methods

Patient selection

This retrospective study was approved by our Institutional Review Board and did not require informed consent. We performed a computerized search of the radiology information system and cardiac procedure record system at our institute for the period May 1, 2004 through April 30, 2009. The computerized search identified all non-dialysis-dependent patients who underwent an unenhanced abdominal CT within 7 days but at least 1 hour after receiving either intra-arterial iodixanol (Visipaque-320, GE Healthcare, Milwaukee, WI) for a coronary artery catheterization or intravenous iodixanol for an abdominopelvic CT scan. Patients who were exposed to a second dose of intra-arterial or intravenous contrast material within the delimited interval were excluded. A final population of 166 patients was included in the study. The intra-arterial group consisted of 99 consecutive patients who received intra-arterial iodixanol for conventional coronary angiography. The intravenous group consisted of 67 consecutive patients who received intravenous iodixanol during the initial contrast-enhanced CT scans for various indications. Overall, the study population included 159 males (96%) and 7 females (4%), with ages ranging from 34 to 92 years (mean age of 67 years). The mean time delay from contrast administration until the non-contrast

abdominal CT scans was 58 hours (range, 2 to 175 hours). The cohort demographics are summarized in Table 1. The indications for the initial contrast material-enhanced CT scans in the intravenous group were to evaluate for abdominal pain (n=17); neoplasm (n=17); abscess or infection (n=17); chest pain (n=12); altered mental status (n=3); or possible hemorrhage (n=1). The indications for the follow-up non-contrast CT scans in the intravenous group were to evaluate for abdominal pain (n=21); neoplasm (n=15); CT-guidance for a procedure (n=15); possible bleed (n=9); abscess or infection (n=6); and pre-operative screening (n=1). The indications for the post-angiography non-contrast CT scans in the intra-arterial group were to evaluate for possible hemorrhage (n=66); pre-operative screening for cardiothoracic surgery (n=20); neoplasm (n=7); or abdominal pain (n=6).

Coronary angiography & CT techniques

Coronary angiography with or without percutaneous coronary intervention was performed according to practice standards at our institute. Briefly, all 99 patients in the intra-arterial group received midazolam and fentanyl for conscious sedation. Arterial access was achieved in the left or right femoral artery with the insertion of an arterial sheath via the modified Seldinger technique. Coronary vessels were visualized in multiple projections. If percutaneous coronary intervention was warranted, patient was given heparin to optimize the pre-procedural activated clotting time before balloon pre-dilation and stent deployment at the lesion sites. Finally, a Perclose Pro-Glide closure was deployed at the femoral arteriotomy to achieve hemostasis. The mean total volume of intra-arterial iodixanol-320 for coronary angiography was 209 mL (range 50 to 580 mL).

All CT studies were performed using a 16 or 64 detector row CT scanner (LightSpeed, GE Healthcare, Milwaukee, WI), with 2.5-mm or 5-mm axial slice thickness and tube potential of 120 kVp. For the contrast-enhanced CT, patients received a mean intravenous dose of 124 mL iodixanol (range 100 to 186 mL). The iodixanol formulation was identical for every patient and contained an iodine concentration of 320 mg I/mL.

For both the intra-arterial and intravenous groups, pre-procedure and/or post-procedure hydration was not standardized. For varied reasons within 2 days before undergoing the contrast medium-enhanced procedure, 19 out of 99 patients in the intra-arterial group received isotonic saline hydration, whereas 22 out of 67 patients in the intravenous group received similar hydration. Prophylactic measures with sodium bicarbonate and/or administration of *N*-acetylcysteine were selectively given to a few patients in each group (Table 1). For those who received prophylaxis, sodium bicarbonate (154 mEq in Dextrose 5% in water) was typically infused intravenously at 3 mL/kg of body weight per hour for 1 hour prior to contrast administration, while *N*-acetylcysteine (20% solution, 3 mL) was given as an oral dose of 600 mg every 12 hours on the day before and the day of contrast administration.

Image interpretation

A compilation of the non-contrast abdominal CT scans from all 166 patients was presented in random sequence to two attending specialty-trained abdominal radiologists. Unaware of the route of previous contrast administration, both radiologists by consensus reviewed the non-contrast scans on a picture archiving and communication system (PACS) workstation (Impax; Agfa, Mortsel, Belgium). First, the presence of any renal enhancement was assessed qualitatively, and the distribution of persistent enhancement was classified into three patterns: global, cortical, and striated (Figure 1). The global pattern was defined as showing homogeneous enhancement throughout the entire kidney without corticomedullary differentiation. The cortical pattern consisted of uniform opacification of the renal cortex that was clearly distinct from the relatively un-opacified regions of the medulla (3, 11). The

striated pattern was assigned when the enhancement was diffuse throughout the renal parenchyma without corticomedullary distinction but with extensive irregular bands of enhancement or non-enhancement extending through the cortex and medulla.

After qualitative assessment, the CT attenuation of the renal parenchyma in Hounsfield units (HU) was recorded. For all patients, the renal parenchymal CT attenuation was recorded as the mean attenuation of six manually placed elliptical regions of interest (ROI, each 1 ± 0.05 cm² in size), where one ROI was placed in a representative portion of the upper, mid and lower pole of each kidney. For the CT scans with a cortical pattern of persistent enhancement, regions of interest were placed in representative locations of the renal cortex. For the CT scans with a striated pattern of persistent enhancement, regions of interest were placed in areas of relatively homogeneously enhancing parenchyma with care to avoid areas of noticeably hyper- or hypo-enhancing parenchyma. Based on prior studies, persistent renal enhancement was considered to be present when the mean CT attenuation of the renal parenchyma was greater than 55 HU (6, 7).

Chart review

Review of the clinical medical records was performed to obtain relevant patient histories, including age, gender, weight, and diagnoses of chronic renal insufficiency, diabetes mellitus, left ventricular ejection fraction as determined by echocardiogram, congestive heart failure, anemia, and coronary artery disease (Table 1). Hydration and prophylactic regimens previously mentioned were also noted from the medical records. Any adverse event attributed to contrast administration was documented.

Pre- and post-procedural serum creatinine values were recorded. The pre-procedure serum creatinine value measured closest in time to the contrast-enhanced examination (angiography or contrast-enhanced CT) was recorded, and the mean time duration until the procedure was 17 hours (range 0.2 to 347 hours). The post-procedure serum creatinine was recorded as the maximum creatinine level measured within 5 days after the initial contrast administration and prior to any subsequent doses of contrast material. Contrast-induced nephropathy was defined as an absolute increase in serum creatinine concentration of at least 0.5 mg/dL (44.2 μ mol/L) (12, 13). In our study, we judged estimated glomerular filtration rates (eGFR) to be a suboptimal alternative to serum creatinine for evaluating renal function because the most accepted eGFR calculations are known to be inaccurate for patients with normal or only mildly impaired renal function (14), which comprise the majority of the patients in our study, and because the majority of published studies on contrast induced nephropathy utilize serum creatinine as the measure of renal function (2).

Statistical analysis

Fisher's exact test and the unpaired *t*-test were used for the comparison of demographics, clinical profiles, and procedural components between the intra-arterial and intravenous groups. Univariate correlation for the presence of persistent renal enhancement with potential risk factors was also analyzed by Fisher's exact test and Student's *t*-test. Similarly, these two methods were used to analyze the relationship between persistent renal enhancement and contrast-induced nephropathy.

A multivariate logistical regression model was performed with the presence of persistent renal enhancement as the outcome variable, and days between scans, age, contrast volume, and baseline serum creatinine as the predictors. The predictors were selected for use in the multivariate analysis if their univariate *p*-value was less than 0.1. All statistical analyses were calculated with Stata software package, version 8.0 (Stata, College Station, TX). The conventional *p*-value < 0.05 was considered to be statistically significant.

Results

Demographics (Table 1)

The patient demographics are shown in Table 1. There were no significant differences in the mean age or gender distribution between the intra-arterial and intravenous group (67 versus 69 years, respectively, $p > 0.05$; and 95% versus 96% men, respectively, $p > 0.05$).

Compared to the intravenous group, patients in the intra-arterial group had a higher mean weight (86.3 versus 78.9 kg, respectively, $p < 0.001$). A higher mean weight-adjusted dose of contrast material was administered for the intra-arterial procedures than for the intravenous contrast-enhanced CT (777 versus 545 mg I/kg, respectively, $p < 0.001$). The mean elapsed time between coronary angiography and the subsequent non-contrast abdominal CT was shorter than the time elapsed after intravenous contrast-enhanced CT (44.7 versus 78.5 hours, respectively, $p < 0.001$) (Table 1).

Appearance of persistent renal enhancement

Qualitative assessment (Table 2) showed that persistent renal enhancement was more frequently seen in patients who had intra-arterial (58 of 99 patients, or 59%) than intravenous iodixanol administration (23 of 67, or 34%, $p < 0.005$ by Fisher's exact test). Furthermore, the distribution of renal enhancement patterns differed between patients who had intra-arterial versus intravenous contrast materials ($p < 0.01$). In both groups, the most common pattern of persistent renal enhancement was global (33 of 99 patients, or 33%, in the intra-arterial group; and 16 of 67, or 24%, in the intravenous group), and the next commonest pattern was cortical enhancement (20 of 99 patients, or 20%, in the intra-arterial group, 7 of 67, or 10%, in the intravenous group). The striated pattern of persistent enhancement was seen only in patients after intra-arterial contrast administration (4 patients, or 4%).

Quantitative measurement of renal parenchymal attenuation (Table 2) showed that the frequency of persistent renal enhancement, defined as a renal parenchymal CT attenuation value > 55 HU, was significantly higher for the patients receiving intra-arterial contrast material (observed in 54 of 99 patients, or 55%) than for those receiving intravenous contrast material (observed in 21 of 67 patients, or 31%, $p < 0.005$). Similarly, marked persistent enhancement, defined as a CT value > 100 HU, was noted with higher frequency for the patients receiving intra-arterial (17 of 99 patients, or 17%) than for those receiving intravenous contrast material (3 of 67 patients, or 4%, $p < 0.05$). The qualitative enhancement patterns observed in these 20 patients with severe enhancement were global ($n=10$), cortical ($n=9$), and striated ($n=1$).

Predictors of persistent renal enhancement

The predictors for finding persistent renal enhancement > 55 HU are shown in Table 3. Overall, the renal parenchymal CT attenuation on the non-contrast CT was inversely related to the time delay between the contrast-enhanced procedures and the subsequent non-contrast CT (Figure 2, Table 3), but were not clearly different among the different patterns of renal enhancement. Higher renal attenuation measurements were observed in patients who received larger doses of contrast administered during either coronary angiography or contrast enhanced CT (Figure 3, Table 3). Patients with persistent renal enhancement had a higher average baseline serum creatinine (1.33 mg/dL) than those without enhancement (1.16 mg/dL, $p < 0.001$).

A multivariate logistical regression model showed that independent predictors of the presence of persistent renal CT enhancement > 55 HU after intravascular administration of iodixanol were: 1) a shorter time interval between the initial contrast material administration

and the unenhanced CT scan; 2) a larger contrast material dose; 3) a higher baseline serum creatinine level; and 4) older age (Table 4). The route of iodixanol administration did not predict the presence of persistent renal enhancement ($p > 0.5$). More specifically, the likelihood of detecting the presence of renal enhancement at delayed CT decreased by 48% for each additional day from the initial contrast exposure (odds ratio 0.52, $p < 0.001$). Likelihood of detecting persistent renal enhancement increased by 10% for every 10 mL increase in contrast volume administered (odds ratio 1.10, $p < 0.001$). For each 1 mg/dL increase in baseline serum creatinine level, there was an 8.9 times-increase in probability of observing persistent renal enhancement (odds ratio 8.90, $p = 0.005$). For an increase in age by one decade, the likelihood of detecting persistent renal enhancement increased by 61% (odds ratio 1.61, $p = 0.030$).

Contrast-induced nephropathy

Contrast-induced nephropathy, defined as a 0.5 mg/dL rise or more in serum creatinine level, was noted in 12 patients (7%) overall (Tables 5 and 6). Nine of these patients received intra-arterial iodixanol (9% of intra-arterial group), and three received intravenous iodixanol (4% of intravenous group). Univariate analysis (Table 5) suggested various predisposing factors for contrast-induced nephropathy, including older age, higher baseline creatinine, and longer time at which the post-exposure creatinine was measured ($p < 0.05$ for each). The route of contrast administration was not statistically significant in predicting contrast-induced nephropathy in this model ($p = 0.366$). Post-exposure serum creatinine levels were measured an average of 57 hours after intra-arterial contrast administration and an average of 60 hours after intravenous contrast administration (Table 1). In the intra-arterial group, 17 patients (17%) had only one follow-up creatinine value available, collected within 24 hours of cardiac catheterization. In the intravenous group, 2 patients (3%) had only available creatinine values within 24 hours after contrast-enhanced CT.

In the intra-arterial group, 2 of the 9 patients who developed contrast-induced nephropathy progressed to renal failure requiring hemodialysis. One of the 2 patients was started on dialysis 3 days after his coronary angiography, the dialysis was continued for 6 days after which point it was stopped due to recovery of baseline renal function. The other patient was started on dialysis 13 days after the coronary angiography and died a month later due to a ruptured aortic aneurysm. In the intravenous group, 1 of the 3 patients with contrast-induced nephropathy required hemodialysis; this patient was started on hemodialysis 11 days after the contrast enhanced CT and died 4 months later due to multi-organ failure.

CIN developed in a higher proportion of patients with (10 of 75, or 13%) than in those without persistent renal enhancement on the non-contrast CT (2 of 91, or 2%, $p < 0.01$, Table 4), where persistent renal enhancement was defined as a renal parenchymal CT attenuation greater than 55 HU. The proportion of patients with contrast-induced nephropathy increased to 30% (6 out of 20) in patients with a renal parenchymal attenuation greater than 100 HU at the time of the non-contrast CT scans. Details regarding the 12 patients with contrast-induced nephropathy are listed in Table 7. Among these 12 patients, 10 had persistent renal enhancement on non-contrast abdominal CT, 4 of whom demonstrated persistent enhancement > 55 HU three or more days after intra-arterial administration of iodixanol (Patients No. 5–7, 9).

Of the 10 patients with persistent renal enhancement, a global renal enhancement pattern was observed in 4 patients; a cortical pattern was observed in 4 patients; whereas a striated pattern was observed in 2 patients (Figure 4). Specifically in the intra-arterial group, there were 4 patients with cortical, 2 with global, and 2 with striated pattern of persistent renal enhancement out of the 9 patients with contrast-induced nephropathy. In the intravenous

group among the 3 patients with contrast-induced nephropathy, 1 patient had global renal enhancement and 1 patient had cortical enhancement.

Discussion

We found that after iodixanol administration for conventional coronary angiography or contrast enhanced CT, renal parenchymal enhancement can persist and be seen by non-contrast CT for 7 days or longer. While the presence and intensity of delayed renal parenchymal enhancement is loosely associated with an intra-arterial route of contrast material administration at simple univariate analysis, our multivariate model showed that the route of contrast material administration was not an independent predictor of delayed renal enhancement. Instead, a high dose of contrast material, short time delay to non-contrast CT imaging, high baseline serum creatinine, and older age were the primary predictors of finding persistent renal parenchymal enhancement. In other words, while persistent renal enhancement was seen more frequently and intensely in patients who had undergone coronary angiography, the enhancement was primarily due to use of a higher dose of contrast and a shorter time interval between the intra-arterial administration of contrast and the subsequent non-contrast CT.

Our findings also contribute data to the poorly studied question regarding whether an intra-arterial versus intravenous route of contrast material administration contributes to renal injury. Similar to what was found in prior studies (6, 11), we found that the vast majority of patients with persistent renal parenchymal enhancement, regardless of the route of contrast material administration, displayed either global renal parenchymal enhancement or diffuse cortical enhancement, and that these patterns of enhancement were not associated with CIN. However, we also observed another pattern of persistent renal enhancement, which we described as striated and which was only seen after coronary angiography. While the underlying mechanism for this striated pattern was not clear, we speculate that a possible explanation for the striated wedge-shaped or segmental hyper- or hypo attenuation appearance may be related to multiple segmental infarcts from micro-emboli during mechanical catheterization of the aorta or heart proximal to the renal arteries. Importantly, 2 of the 4 patients with the striated pattern of enhancement (50%) subsequently developed CIN. Further study of this type of persistent renal enhancement pattern in larger patient populations will be useful to assess whether it is truly associated with renal injury.

As noted above, our finding of a loose association between persistent renal enhancement at CT and the development of CIN builds on the findings of prior studies. In a cohort of 16 diabetic patients and additional normal volunteers who underwent intravenous or intra-arterial contrast material, Jakobsen and colleagues observed persistent renal cortical CT enhancement in chronic renal failure patients, but none had significant changes in their GFR after contrast administration (9, 10, 15). In a study of 50 patients who received iohexol or diatrizoate and imaged by non-contrast CT one day later, Love and colleagues reported that their only patient who had persistent renal enhancement > 100 HU subsequently developed contrast-induced nephropathy (6). Our results are also in agreement with those of Yamazaki et al who found that a slightly higher incidence of CIN was seen in patients with intense persistent renal enhancement on non-contrast CT scans obtained 1 day after conventional angiography (CIN developed in 2 of 49 patients) compared with those without intense enhancement (CIN developed in 6 of 221 patients) (7). Our results build on prior works in two ways. First, we studied a relatively large number of patients with either intra-arterial or intravenous contrast material, all of whom received iodixanol. Secondly, we evaluated time points ranging from 1.4 to 175.7 hours after contrast administration, which reflects the practice pattern in our hospital rather than an arbitrary time point 1 day after contrast administration. Our data was therefore amenable to a multiple regression model which

clearly shows the multi-factorial nature of finding delayed renal enhancement, which relates to a shorter time lag from the contrast administration to the unenhanced CT, higher dose of contrast material, and elevated baseline serum creatinine. Notably, these predictors of persistent renal enhancement are the same as those that predispose patients to contrast-induced nephropathy, and a more intense persistent renal enhancement is not a particularly strong prognosticator of worsened renal outcome.

Our study has several limitations. Firstly, all patients in our study received iodixanol, which is an isoosmolar nonionic dimeric contrast material that is associated with a higher incidence of prolonged nephrograms than other nonionic iodinated contrast materials (10, 11, 15). While the pharmacokinetics of iodixanol are similar to those of other commercially available iodinated contrast material (16, 17), and the clinical and renal toxicity of iodixanol has been shown to be similar to or better than that of other non-ionic contrast materials (9, 10, 15–20), our findings may reflect a relatively high rate of prolonged renal enhancement compared to what would have been observed with other non-ionic contrast materials. While no clinical sequela has been ascribed to the association between iodixanol administration and prolonged nephrograms, two recent studies in rats associated iodixanol administration with increased urine viscosity and upregulation of renal injury biomarkers (21, 22).. A second important limitation to recognize about our study is that it was neither intended nor powered to find a difference in the incidence of CIN between intra-arterial and intravenous contrast material administration (13), but rather focused on the significance of the common finding delayed renal parenchymal enhancement. A larger prior comparison of 430 patients receiving intra-arterial versus 499 receiving intravenous contrast material showed a 3.44 times increased risk of contrast-induced nephropathy in patients receiving intra-arterial contrast materials (23). Though a higher percentage of our patients who received intra-arterial versus intravenous contrast material developed CIN, this difference was not statistically significant. In addition, in our study, serum creatinine levels after angiography were often obtained within 24 hours post-procedure. Because serum creatinine can rise up to 48 hours after contrast administration and maintain for 2–5 days, it is likely that we have under-estimated the incidence of contrast-induced nephropathy in the intra-arterial contrast administration arm since no serum creatinine value was available beyond 24 hours and within 120 hours post-contrast in many patients. A third limitation of our study is that, much like prior reports, the intra-arterial and intravenous patient groups were not matched for the prevalence of coronary artery disease, weight, dose of contrast material administered, nor time delay to non-enhanced CT. Nevertheless, we evaluated for the effect of left ventricular ejection fraction and congestive heart failure within and between groups and did not find an association between these clinical predictors and the prevalence of either delayed renal enhancement or CIN. Fourthly, since our study was performed at a Veterans Affairs site, women are underrepresented in our patient sample. Nevertheless, our patient population reflects that of a clinically relevant hospital practice where follow-up CT scans are obtained for clinical indications, rather than artificial, reasons.

Persistent renal enhancement at follow-up non-contrast CT suggests a greater risk for contrast-induced nephropathy, but the increased frequency of striking renal enhancement in patients who received intra-arterial rather than intravenous contrast material also reflects the larger doses of contrast and shorter time to subsequent follow-up CT scanning for such patients. Other contributing factors to persistent renal enhancement include a higher baseline serum creatinine and increased age. Whether the route of iodixanol delivery contributes to contrast-induced nephropathy requires a more sufficiently powered study.

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Figure 1. Three patterns of persistent renal enhancement observed at the delayed non-contrast CT. A) Global distribution without corticomedullary differentiation; B) Cortical distribution with clear distinction between enhanced renal cortices and un-enhanced renal medulla; C) Striated distribution with wedge-shaped enhancing and hypoenhancing segments.

Figure 2.

Graph of renal parenchymal CT attenuation at non-contrast CT scans obtained for each day after intravenous or intra-arterial iodixanol administration. A shorter elapsed time between intravascular contrast administration and subsequent non-contrast CT correlated with increased magnitude of delayed renal enhancement ($r = -0.30$, $p < 0.001$). Also, while intra-arterial administration of contrast material showed a greater magnitude of delayed renal enhancement than did intravenous for each day of time lapse, multivariate analysis (Table 6) showed that this difference was not statistically independent from the volume of contrast material that was administered.

Figure 3. Renal parenchymal CT attenuation on the non-contrast CT scans versus intravascular contrast material volume. Larger volumes of administered contrast material correlated with increased persistent enhancement of the renal parenchyma ($r = 0.23$, $p < 0.001$)

Figure 4.

Persistent non-contrast abdominal CT scans from selected patients in the contrast-induced nephropathy group. Each patient received either intra-arterial or intravenous iodixanol previously. Refer to Table 5 for specific procedural and patient information. **A)** Patient No. 2 with cortical contrast retention; **B)** Patient No. 3 with global enhancement; **C)** Patient No. 5 with striated pattern; **D)** Patient No. 7 with cortical retention; **E)** Patient No. 11 with cortical retention; **F)** Patient No. 12 with striated pattern

Table 1

Baseline patient clinical and procedural characteristics for those who received iodixanol intra-arterially for cardiac catheterization or intravenously for contrast-enhanced CT scans. Mean values for continuous variables are listed as the mean±standard deviation, with the range in parentheses where applicable.

Parameters	Intra-arterial (n = 99)	Intravenous (n = 67)	p-value
<u>Demographics</u>			
Age in years (range)	67±10 (47 to 92)	69±12 (34 to 86)	0.179
Men	95 (96%)	64 (96%)	1.000
Weight in kg	86.3±19.6 (50.2 to 151.2)	78.9±20.4 (40.4 to 144.0)	< 0.05
<u>Contrast administration</u>			
Contrast volume in mL (range)	209±129 (50 to 580)	124±13 (100 to 186)	< 0.001
Iodine load per body weight in g/kg	0.78±0.45 (0.19 to 2.43)	0.55±0.15 (0.27 to 0.95)	< 0.001
Time delay from contrast administration to non-contrast CT in hours (range)	44.7±46.2 (2.3 to 175.7)	78.5±45.0 (1.4 to 170.3)	< 0.001
<u>Clinical data</u>			
Baseline serum creatinine (SCr) in mg/dL	1.25±0.35 (0.58 to 2.40)	1.22±0.29 (0.50 to 1.78)	0.600
Post-exposure SCr in mg/dL	1.36±0.54 (0.70 to 3.39)	1.27±0.38 (0.62 to 2.26)	0.261
Time from contrast administration to post-exposure SCr in hrs	57.0±32.9 (5.2 to 119.8)	60.5±28.7 (6.8 to 119.5)	0.491
Absolute change in SCr in mg/dL	0.10±0.38 (−0.70 to 1.99)	0.04±0.27 (−0.60 to 0.87)	0.310
Chronic kidney disease	25 (25%)	24 (36%)	0.167
Diabetes mellitus	39 (39%)	19 (28%)	0.184
Hypertension	82 (83%)	51 (76%)	0.325
Congestive heart failure	28 (28%)	10 (15%)	0.059
Anemia	17 (17%)	15 (22%)	0.428
Coronary artery disease	96 (97%)	16 (24%)	< 0.001
Ejection fraction	52.8±15.4 (13.8 to 82.9)	62.0±12.3 (40.0 to 82.0)	< 0.005
Sodium bicarbonate prophylaxis only	4 (4%)	17 (25%)	< 0.001
N-acetylcysteine prophylaxis only	6 (6%)	5 (7%)	0.326
Sodium bicarbonate & N-acetylcysteine prophylaxis	33 (33%)	23 (34%)	1.000

Table 2

CT findings at non-enhanced CT following prior intra-arterial or intravenous administration of iodixanol. Fishers exact test showed that the distribution of persistent renal enhancement pattern was significantly different between patients who received intra-arterial versus intravenous contrast. Similarly, the frequency of persistent renal enhancement with renal parenchymal CT values > 55 HU and > 100 HU was significantly higher for patients receiving intra-arterial than for those receiving intravenous contrast material. However, the elapsed time between contrast administration and subsequent non-enhanced CT was significantly shorter for patients receiving intra-arterial than those receiving intravenous contrast material.

Imaging findings at non-enhanced CT	Intra-arterial (n = 99)	Intravenous (n = 67)	p-value
Qualitative pattern of persistent enhancement			
None	41 (41%)	44 (66%)	< 0.01
Global	33 (33%)	16 (24%)	
Cortical	21 (21%)	7 (10%)	
Striated	4 (4%)	0 (0%)	
Renal parenchymal CT attenuation in HU (range)	73.7±49.3 (27 to 344)	51.8±23.8 (28 to 156)	< 0.001
Presence of persistent renal enhancement (HU > 55)	54 (55%)	21 (31%)	< 0.005
Presence of severe persistent renal enhancement (HU > 100)	17 (17%)	3 (4%)	< 0.05
For patients with persistent renal enhancement (HU > 55), time from contrast exposure to non-enhanced CT in hours (range)	28.3±33.6 (2.3 to 150.1)	52.4±44.8 (1.4 to 170.3)	< 0.05

Table 3

Univariate analysis of baseline characteristics for the outcome of persistent renal parenchymal enhancement as defined by a quantitative CT attenuation measurement > 55 HU. Mean values were determined by unpaired t-tests for age, contrast volume, absolute change in serum creatinine, and time from contrast administration to delayed non-contrast CT. Frequency was compared by Fisher's exact test for gender and route of contrast administration.

	Persistent renal enhancement (n = 75)	No persistent renal enhancement (n = 91)	p-value
Gender			
Men (n = 159)	72	87	
Women (n = 7)	3	4	1.000
Age (years)	69±12 (34 to 92)	66±11 (43 to 89)	0.077
Contrast volume (mL)	227.3±131.4 (60 to 580)	135.9±64.1 (50 to 440)	< 0.001
Baseline serum creatinine (SCr) (mg/dL)	1.33±0.37 (0.60 to 2.40)	1.16±0.26 (0.50 to 1.78)	< 0.001
Absolute change in SCr (mg/dL)	0.14±0.42 (-0.7 to 1.99)	0.03±0.24 (-0.6 to 0.73)	< 0.05
Time from contrast administration to delayed non-contrast CT (hrs)	35.1±38.3 (1.4 to 170.3)	77.6±47.7 (2.3 to 175.7)	< 0.001
Ejection Fraction*	55.1±15.6 (23 to 82.9)	57.3±14.3 (13.8 to 81.3)	0.4212
Route of contrast administration			
Intra-arterial (n = 99)	54 (72%)	45 (49%)	
Intravenous (n = 67)	21 (28%)	46 (51%)	<0.005

Data are presented as mean±SD with range in parentheses where appropriate.

* Ejection fraction available for only 50 patients with and 58 without persistent renal enhancement

Table 4

Multivariate logistic regression model for predictors of persistent renal enhancement. Independent predictors of persistent renal enhancement on a non-enhanced CT scan included a shorter time interval between the administration of contrast material and the non-enhanced CT scan, a larger administered contrast material volume, a higher baseline serum creatinine level, and older age. The gender and route of contrast material (intra-arterial versus intravenous) were not found to be independent predictors of persistent renal enhancement.

	Odds Ratio	p-value	95% CI
Time interval between contrast material administration and non-contrast CT (days)	0.52	< 0.001	0.383~0.706
Contrast material volume (10 mL)	1.10	< 0.001	1.042~1.152
Baseline serum creatinine (mg/dL)	8.90	< 0.005	1.908~41.56
Age (decades)	1.61	< 0.05	1.046~2.484
Male gender	0.35	0.286	0.052~2.391
Intra-arterial route of contrast material administration	1.08	0.872	0.412~2.843

Table 5

Univariate analysis of pre-contrast administration predictors for the outcome of contrast-induced nephropathy (CIN), defined as an absolute increase in serum creatinine by at least 0.5 mg/dL

	CIN (n = 12)	No CIN (n = 154)	<i>p</i> -value [*]
Gender			
Men (n = 159)	12	147	
Women (n = 7)	0	7	1.000
Age (years)	74±7 (58 to 85)	67±11 (34 to 92)	< 0.05
Contrast volume (mL)	242.7±141.0 (75 to 515)	176.5±108.7 (50 to 580)	0.061
Baseline serum creatinine (SCr) (mg/dL)	1.56±0.35 (1.07 to 2.06)	1.22±0.32 (0.5 to 2.4)	< 0.001
Post-exposure SCr (mg/dL)	2.48±0.49 (1.80 to 3.39)	1.23±0.34 (0.62 to 2.60)	< 0.001
Absolute change in SCr (mg/dL)	0.92±0.42 (0.50 to 1.99)	0.01±0.21 (-0.70 to 0.43)	< 0.001
Time from contrast administration to post-exposure SCr (hrs)	82.4±32.7 (30.6 to 119.5)	56.4±30.5 (5.2 to 119.8)	< 0.01
Ejection Fraction ^{**}	51.8±16.0 (25 to 78.1)	56.8±14.4 (20.8 to 82.9)	0.2855
Route of contrast administration			
Intra-arterial (n = 99)	9	90	
Intravenous (n = 67)	3	64	0.366

Data are presented as mean±SD with range in parentheses where appropriate.

*
t test

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Ejection fraction available for 11 patients with and 97 without contrast induced nephropathy

Table 6

Association between persistent renal enhancement and contrast-induced nephropathy

	No enhancement (n = 91)	Presence of enhancement (HU > 55) (n = 75)	Severe enhancement (HU > 100) (n = 20)	p-value *
CIN (n = 12)	2 (2%)	10 (13%)	6 (30%)	< 0.01
No CIN (n = 154)	89 (98%)	65 (87%)	14 (70%)	

*
Fisher exact test

Table 7
Procedural and biochemical characteristics of patients identified with contrast-induced nephropathy

Patient No.	Route of contrast administration	Contrast material volume (mL)	Time lag between contrast bolus & non-contrast CT scan (h)	Mean renal parenchymal CT attenuation (HU)	Baseline serum creatinine (mg/dL)	Maximum post-contrast serum creatinine recorded (mg/dL)	Time lag between contrast bolus & post-contrast creatinine measurement (h)
1*	Intravenous	120	126.6	38	1.46	2.10	119.5
2	Intravenous	150	26.8	80	1.76	2.26	60.9
3	Intravenous	120	1.4	156	1.21	2.08	33.6
4	Intra-arterial	75	170.9	27	1.07	1.80	111.5
5*	Intra-arterial	150	150.1	62	2.06	3.28	113.2
6	Intra-arterial	125	92.7	75	1.71	2.46	101.2
7	Intra-arterial	400	106.7	88	1.48	2.14	103.1
8	Intra-arterial	290	50.9	108	2.00	2.50	93.2
9	Intra-arterial	170	146.1	118	1.40	2.60	109.3
10*	Intra-arterial	350	12.6	148	2.01	2.93	61.4
11	Intra-arterial	515	40.0	174	1.10	2.20	30.6
12	Intra-arterial	325	53.7	185	1.40	3.39	50.7

* Patients received subsequent hemodialysis secondary to declining renal function.