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ORIGINAL ARTICLE

Persistent CT nephrograms following cardiac catheterisation and intervention: initial observations

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Abstract
Objectives To describe persistent nephrographic patterns detected by unenhanced renal CT at 24 h after cardiac catheterisation and intervention.
Methods This prospective study was Health Insurance Portability and Accountability Act-compliant and institutional review board approved. Twenty-nine patients (20 men, nine women; average age 63.27 and range 41–85 years) agreed to undergo unenhanced dual-energy computed tomography (CT) limited to their kidneys at 24 h after cardiac catheterisation. CT attenuation values (Hounsfield units) were made from the cortical and medullary regions and single kidney total parenchymal iodine values (milligrams) were measured. Spearman's rank correlation coefficient and a two-sided Fisher's exact test were used in the statistics.
Results Focal nephrograms were observed in at least one kidney (range, one to five regions per kidney) in 10/29 (34%) of patients and bilateral global nephrograms in 13/29 (45%) of patients. Focal nephrograms correlated with cardiac catheterisation fluoroscopic time (r=0.48; P=0.0087). For global nephrograms, the total iodine content of right and left kidneys correlated with fluoroscopic time (r=0.79 and 0.76; P<0.0001, respectively) and the amount of contrast material (CM) used (r=0.77 and r=0.74; P<0.0001, respectively).
Conclusion Persistent focal and global nephrograms occur commonly as assessed by non-contrast CT at 24 h post cardiac catheterisation and our observations suggest they could be related to procedural factors.

Keywords Cardiac · Interventional · Urogenital · Contrast media · CT

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Introduction

Recent clinical commentaries suggest that acute kidney injury (AKI) is more likely to occur following cardiac catheterisation and intervention than with contrast-enhanced computed tomography (CECT), especially in renally compromised patients [1, 2]. Some have questioned whether the differential rates of AKI are the result of contrast-induced nephropathy (CIN) or factors related to the cardiac catheterisation procedure itself, and/or the greater degrees of pre-existing comorbidities found in patients with

cardiac disease [1–5]. Post cardiac catheterisation cerebral emboli have been described in up to 15% of patients detected by transcranial Doppler and diffusion-weighted magnetic resonance imaging (MRI) [6, 7] and myocardial microinfarcts in 28% detected by MR [8–10]. We are not aware of any imaging studies that have assessed possible analogous renal complications, although they would seemingly be likely to occur.

Focal, segmental nephrograms on delayed CT scans have been uncommonly reported, but are believed to be a possible indication of AKI, related to focal renal ischemia. Yamazaki et al. [11] and Monsky et al. [12] observed segmental, wedge-shaped nephrograms, as well as global nephrograms on delayed CT scans following transarterial chemoembolisation (TACE), with the global nephrograms being associated with AKI. Monsky et al. [12] postulated that the delayed CT segmental nephrograms could represent foci of renal injury secondary to renal emboli related to the catheterisation procedure itself.

Other studies have suggested that a persistent nephrogram is an indicator of significant AKI. Older et al. [13] and Love et al. [14] reported that persistent, bilateral and global nephrograms detected by either plain radiography or delayed CT are indicative of acute renal failure (ARF) related to CIN.

The meaning remains unclear whether there is a correlation with the incidence of CIN or cardiac catheterisation. We describe the 24-h delayed nephrographic CT findings and compare these with procedure time, amount of contrast material (CM) administered and changes in the serum creatinine (SCr).

Materials and methods

Patient selection

This prospective Health Insurance Portability and Accountability Act-compliant study was approved by our institutional review board. Between June 2010 and January 2011, 124 patients were approached at random to participate in the study prior to their cardiac catheterisation procedure at our institution. Patients were asked if they would be willing to undergo a limited dual energy CT scan of their kidneys 24 h after their cardiac catheterisation procedure to assess the possible persistence of CM (nephrogram) in their kidneys. Patient selection was also based on their willingness to acquire a SCr at 48–72 h post procedure. Exclusion criteria were subjects younger than 18 years old, an estimated glomerular filtration rate (eGFR; Modified Diet in Renal Disease estimation) [15] <60 ml/min, having undergone or being scheduled to undergo any other radiographic procedures requiring iodinated contrast media from 72 h before to 72 h after the cardiac catheterisation procedure, having a hypersensitivity to iodine-containing contrast media requiring prophylactic medication, or being pregnant or lactating females. Eighty-nine patients were initially excluded for the following reasons: 72 declined the consent or were unable to comply with follow-up 48–72 h SCr; ten had an eGFR<60 ml/min; four had another scheduled contrast medium study; two had a history of contrast medium hypersensitivity requiring prophylactic premedication. From the resulting patients, 35 were enrolled following signed informed consent for the 24-h delayed CT examination. Three patients did not appear for CT, the CT system was not available in one case, one patient withdrew consent and one patient had a change in treatment after enrollment. Thus, 29 patients completed the 24-h CT protocol (Table 1). An increase in SCr from baseline values of ≥44 μmol/l (0.5 mg/dl) or ≥25% were recorded as changes in renal function significant enough to be classified as CIN as defined by the European Society of Urogenital Radiology [16].

Cardiac catheterisation procedures

Patients were selected for cardiac catheterisation based on clinical signs and symptoms of chest pain consistent with angina. All patients had baseline blood tests to include a complete blood count (CBC), chemistry panel and prothrombin time–international normalised ratio (PT-INR) before angiography. Included in the preliminary clinical assessment were baseline serum creatinine and blood urea nitrogen (BUN).

Informed consent for the cardiac catheterisation procedure was acquired following the discussion of risks, benefits, complications and alternatives to the procedure. The patients were brought to the catheterisation laboratory in a fasting state. In patients with an eGFR≥60 ml/min, there is no routine pre-medication or hydration protocol used. Intravenous fentanyl, midazolam and inapsine were used for sedation. Lidocaine 1% without epinephrine was used for local anesthesia. Visipaque (Iodixanol, 320 mgI/ml; osmolality 290 mOsm/kg and viscosity 11.8 cps at 37°C; GE Healthcare, Princeton, New Jersey) was the contrast medium in all cases. Arterial access from either the femoral artery or the radial artery was obtained using a modified Seldinger technique, with or without ultrasound guidance.

At the completion of the procedure, the total CM utilised and the total amount of fluoroscopy time was recorded and documented. Patients had their catheter sheaths discontinued when their activated partial thromboplastin time (aPTT) was less than 50 s or their ACT was less than 180 s and remained in the supine position for variable amounts of time, depending on whether or not a closure device was placed. Radial

Table 1 Clinical parameters

Patient number	Age	Gender	Intervention	Total contrast (ml Visipaque)	Total fluoro time[a]	Baseline eGFR[b] (ml/min/1.73 m^2)	SCr data[c]		
							Baseline	24 h	48-72 h
1	65	M	Angioplasty and stent	240	17.00	80	83.60 (0.95)	101.20 (1.15)	86.24 (0.98)
2	66	M	Angioplasty and stent	300	15.40	74	88.88 (1.01)	88.00 (1.00)	—
3	58	M	None	150	10.10	105	66.88 (0.76)	—	66.00 (0.75)
4	64	M	Balloon angioplasty ×2	270	21.10	67	96.8 (1.10)	97.68 (1.11)	121.44 (1.38)
5	69	F	None	100	6.15	65	76.56 (0.87)	—	93.28 (1.06)
6	56	F	None	100	7.00	80	66.00 (0.75)	—	84.48 (0.96)
7	56	F	Stent	300	20.50	96	56.32 (0.64)	—	60.72 (0.69)
8	51	F	None	150	14.60	85	63.36 (0.72)	60.72 (0.69)	—
9	73	M	None—3 vessel disease, referred for CABG	180	12.30	104	65.12 (0.74)	—	73.92 (0.84)
10	71	M	None	120	3.60	82	80.08 (0.91)	—	90.64 (0.99)
11	71	M	None	130	12.10	76	85.36 (0.97)	88.00 (1.00)	90.64 (1.03)
12	68	M	Rotational atherectomy with stent	370	32.30	68	95.04 (1.08)	—	95.92 (1.09)
13	60	M	None	80	9.50	84	80.96 (0.92)	—	—
14	69	M	3 stents with rotational atherectomy	460	58.60	79	83.60 (0.95)	80.96 (0.92)	96.80 (1.10)
15	68	M	3 stents	325	25.30	68	95.04 (1.08)	80.08 (0.91)	79.20 (0.90)
16	71	M	None	145	10.20	67	95.04 (1.08)	81.84 (0.93)	220.88 (2.51)
17	41	F	None	130	9.60	63	85.36 (0.97)	—	101.2 (1.15)
18	51	M	3 stents	380	33.10	154	49.28 (0.56)	63.36 (0.72)	65.12 (0.74)
19	57	M	Stent	280	32.30	70	95.92 (1.09)	—	107.36 (1.22)
20	66	M	None	150	13.70	88	76.56 (0.87)	69.52 (0.79)	75.68 (0.86)
21	61	M	Stent	180	15.30	92	74.80 (0.85)	72.16 (0.82)	88.88 (1.01)
22	65	F	3 vessel disease, referred for CABG	20	21.00	73	69.52 (0.79)	43.12 (0.49)	66.00 (0.75)
23	85	F	Stent	240	17.30	68	70.470 (0.80)	59.84 (0.68)	63.36 (0.72)
24	56	M	None	77	12.30	93	74.80 (0.85)	74.80 (0.85)	89.76 (1.02)
25	52	F	3 stents	175	29.50	60	86.24 (0.98)	—	87.12 (0.99)
26	65	F	None	90	5.60	63	79.20 (0.90)	—	82.72 (0.94)
27	73	M	None	65	8.40	61	103.84 (1.18)	—	113.52 (1.29)
28	67	M	3 stents	340	35.20	63	101.20 (1.15)	—	95.92 (1.09)
29	60	M	Rotational atherectomy stents ×2, and balloon angioplasty	475	49.00	87	78.32 (0.89)	62.48 (0.71)	—

[a] Fluoroscopy time in minutes

[b] *eGFR* estimated glomerular filtration rate (MDRD equation)

[c] *SCr* serum creatinine μmol/l (mg/dl)

artery access patients had their sheaths removed in the laboratory before returning to the ward. Outpatients having only a diagnostic cardiac catheterisation procedure were sent home on the same day after adequate hemostasis had been obtained at the arterial puncture site. Patients undergoing coronary intervention remained hospitalised overnight for observation as per standard protocol.

CT image acquisition

All CT images were obtained using dual energy CT (DECT) (Somatom-Definition DS, software version VE20: Siemens Healthcare) operated in the dual-energy mode with tube A at 80 kV and 499 mA, tube B at 140 kV and 118 mA (effective milliampere seconds of 714 and 168, respectively), and a collimation of 14×1.2 mm. Two image sets with 5.0-

mm-thick and 1.5-mm-thick sections were reconstructed by using H30 (medium smooth) and D37s (dual-energy, medium sharp) kernels, respectively. Each image set consisted of an 80-kV series, a 140-kV series, and a third series, which combined the 80-kV and 140-kV images to produce a virtual 120-kV image set. The combined images have a higher signal–to-noise ratio than the constituent 80-kV and 140-kV image sets.

Image interpretation

The DECT nephrographic images were independently assessed by three operators. One operator was a radiology resident; one, an interventional radiologist with 20 years of clinical experience; and the third was a genitourinary radiologist with 35 years of clinical experience. Each observer was provided with two nephrographic imaging sets. The first imaging set depicted a grading scale for the global nephrograms, as demonstrated on the combined imaging series (Fig. 1a-d). This included kidneys without a nephrogram, kidneys with a minimally bilaterally dense nephrogram, kidneys with a moderately bilaterally dense nephrogram, and kidneys with a markedly dense bilateral nephrographic pattern. The second imaging set included images of a focal nephrogram (Fig. 2a, b). The observers were also asked to identify whether vicarious excretion of CM was identifiable either by gallbladder opacification or gallbladder and/or gut opacification (Figs. 1b, d and 5a, b). Intraluminal bowel or gallbladder, visually dense material was considered a positive finding. After the readers completed their review of the 29 unenhanced CT studies at 24 h after cardiac catheterisation, they met as a group and finalised the scores by consensus.

Quantitative CT image assessment at 24 h post cardiac catheterisation

Cortical and medullary attenuation

Circular regions of interest (ROIs) for the attenuation values in HU of the cortical and medullary regions of each kidney (29 subjects and 57 kidneys) were acquired by one of the investigators having 20 years of clinical radiology experience from the 120-kV, 5-mm slice thickness CT renal images. The circular ROI, measuring 5 mm in diameter, was applied to similar areas of the posterior upper pole, mid and lower pole for each kidney. The average HU values

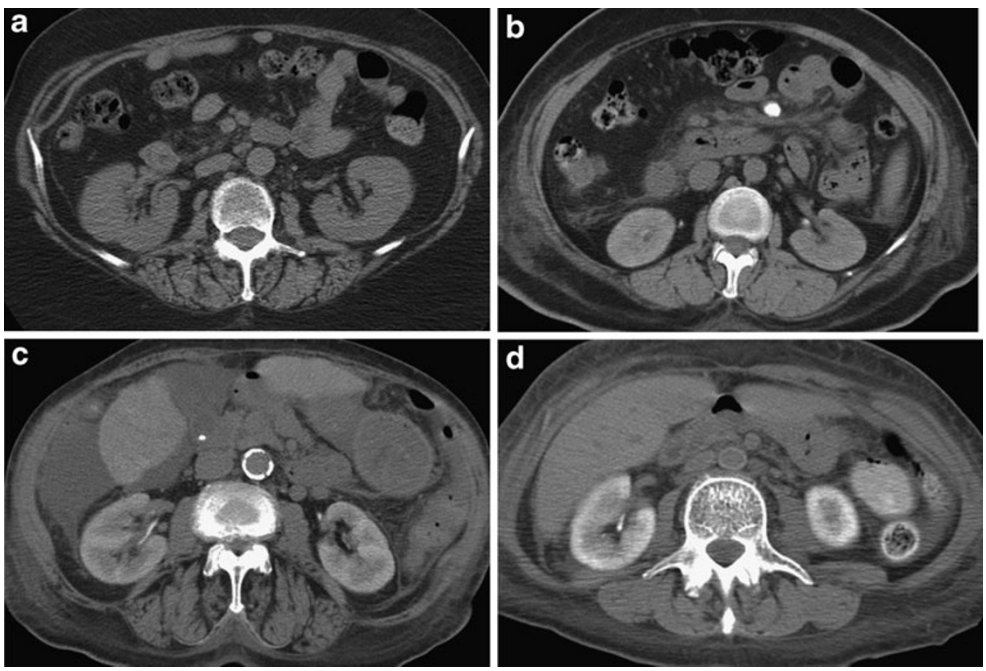

Fig. 1 CT images providing a grading scale for intensity of delayed nephrograms from none to marked. Three ROIs (range 0.2–0.5 cm^2) of anterior, lateral and posterior cortex and the median attenuation values (HU) of right and left kidneys are presented. **a** Axial CT of kidneys in a non-contrast study performed for liver imaging. Abdomen window width and level show the cortical median values 35.2 HU and 34.3 HU, right and left kidneys, respectively. **b** CT nephrograms classified as faint with cortical median values 64.9 HU and 61.8 HU, right and left kidneys, respectively. There is faint vicarious excretion in the ascending colon. Presumed densely calcified lumph node in the mid abdomen was present on prior CT scans. **c** CT nephrograms classified as moderate with cortical median values 91.8 HU and 93.6 HU, right and left, respectively. **d** CT nephrograms classified as marked with cortical median values 156.4 HU and 163.3 HU, right and left kidneys, respectively. Vicarious excretion is noted in the descending colon and small bowel

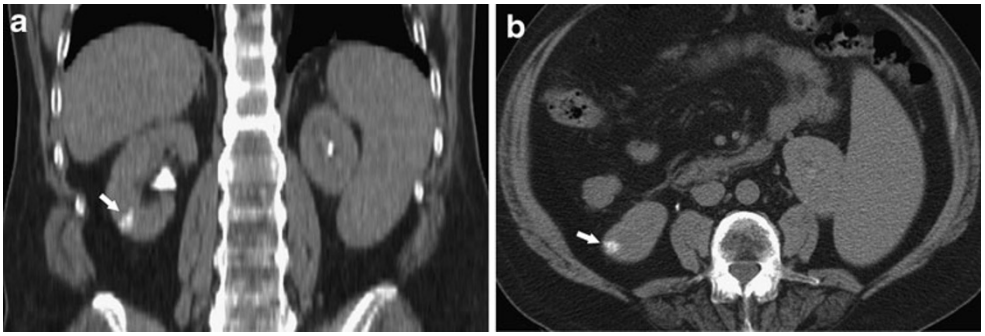

Fig. 2 Coronal (**a**) and axial (**b**) CT images showing a wedge-shaped, peripheral focal nephrogram (*arrow*)

were recorded separately for the cortex and medulla of each kidney. Care was taken not to include adjacent tissues. These were acquired without knowledge of the semi-qualitative assessment results or of any of the clinical parameters. The focal, segmented nephrograms were not measured quantitatively since they were often too small for accurate ROI placement.

Single kidney total iodine content

Total renal iodine content in each kidney was derived from the dual energy data using both subtraction and thresholding techniques. The thresholding technique was employed since, some of the dual energy data were inadvertently erased and some subjects were too large for the limited field of view for the 80 kV image acquisition. Of the 29 patients recruited into the study, the complete image data set (80 kV, 140 kV, combined image, and subtraction image) was saved for 18. Of the 18 complete data sets, 12 left kidneys (LKs) and 11 right kidneys (RKs) were in the field of view for dual energy subtraction. These were used as training sets to assess total iodine content of the 11 patients with erased data, as described in the "Electronic supplementary material".

Statistical analysis

Summary statistics are reported as the mean±standard deviation (median, minimum-maximum) for patient age, cortical and medullary attenuation values (Hounsfield units), total kidney iodine, baseline eGFR, amount of CM used and fluoroscopy time for the cardiac catheterisation procedure. Spearman's rank correlation coefficients were used to study the correlation in which we tested the null hypothesis that the correlation coefficient of zero versus the alternative hypothesis that the correlation is not equal to zero. The two-sided Fisher's exact test was used to compare any increase in SCr from baseline values with the occurrence of global nephrograms. A P value<0.05 was considered statistically significant. All analyses were performed with SAS Version 9.2 (SAS Institute, Cary, NC, USA).

Results

The mean patient age was 63.27±8.8 (65, 41–85) years old and with a male-to-female ratio of 20:9 (Table 1). Intervention was performed in 16 subjects (55%) and diagnostic only in 13 subjects (45%), respectively. The femoral approach was used in 27 patients and the radial approach in two patients. The mean baseline eGFR was 79.8±19.1 (76, 60–154) ml/min. Four of 29 (14%) of subjects (nos. 4, 6, 16 and 18; Table 1) showed one or both an increase in SCr of ≥44 μmol/l (0.5 mg/dl) or ≥25%. Two of these subjects showed a persistent nephrogram and two did not. All four subjects had hypertension; three had hyperlipidemia; one had diabetes Type 1; and one had diabetes Type 2. There were no patients deemed to have clinically significant AKI requiring extended hospitalisation, additional medication or dialysis. The mean CM used for the cardiac catheterisation procedure was 213.86±116.0 (180, 65–475) ml and fluoroscopic time 19.2±13.1 (15.3, 3.6-58.6) min (Table 1).

CT image interpretation

One or more focal nephrograms were observed in at least one kidney in 10/29 (34%) patients and 15/57 (26%) kidneys (Table 2; Figs. 3a-c and 4a, b). These ranged from one to five foci per kidney. Global nephrograms were bilateral in all patients and were observed in 13/29 (45%) (Fig. 5a-c). Eight of 29 (27.5%) were faint and 5/29 (17%) were of moderate density. Vicarious CM excretion in gallbladder, gut or both was observed in 21/29 (72%) of patients.

Quantitative CT assessment at 24 h post cardiac catheterisation

The mean right and left renal cortical mean attenuation values were 61.2±24.8 (59, 28.7-153) HU and 60.1±23.1 (60.5, 32–135) HU, respectively (Table 2). The mean right and left medullary mean attenuation values were 42.2±12.9 (41, 2–84) HU and 43.7±12.9 (42, 21.2-78) HU, respectively. The mean single kidney total iodine

Table 2 Nephrogram parameters

	Focal[a]		Global[b]	Cortical and medullary HUs				24-h total iodine	
Patient number	RK	LK	(Both kidneys)	Rt cortex	Left cortex	Rt medulla	Left medulla	RK iodine total (mg)	LK iodine total (mg)
1	1	0	0	59	61	43	31	269.44	247.68
2	0	0	+	78.5	89.6	55	55.6	256.94	266.05
3	0	1	0	52	34.6	32	41	269.9	324.69
4	0	0	+	69	64	42.5	48	277.43	346.08
5	0	0	0	59	56	43	57	109.02	117
6	0	(-)	0	43.1	(no LK)	46	(no LK)	228.61	(no LK)
7	0	0	++	71.4	65.1	44.6	43.1	444.04	401.17
8	0	1	0	48	33	32	33	207.66	208.96
9	0	0	+	82	67	84	70	194.41	205.98
10	0	0	0	36	32	23	22	141.12	146.05
11	0	0	0	52	60	50	52	133.28	89.86
12	2	2	++	81	91	41	44	518.67	458.74
13	0	0	0	43.7	53.9	37.5	47.1	136.97	128.58
14	1	1	++	153	135	70	56	387.87	364.42
15	0	0	+	73	66.7	38	35	191.09	184.62
16	0	0	0	28.7	48	46.1	43	152.15	135.66
17	0	0	0	40	48	21	37	139.1	91.09
18	0	0	+	75.8	73.2	37	39.8	264.52	254.07
19	1	0	0	60	46	36	38	261.07	223.48
20	0	0	0	43	33.8	31.2	21.2	208.93	209.56
21	0	0	0	35.4	39.6	29.8	37.8	196.64	192
22	2	2	+	76	68	41	39	491.18	538.82
23	0	0	++	73	93	57	78	366.73	405.28
24	1	0	0	36	32	34	28	185.25	183.61
25	1	2	+	75	69	42	44	374.81	368.83
26	0	0	0	39	47	46	41	127.12	117.95
27	0	0	0	35	38	32	36	105.98	110.01
28	5	5	++	80	72	40	60	654.74	655.83
29	0	0	+	77	65	48	45	312.07	308.93

[a] *0* none; *1*, *3*… focal areas for each kidney

[b] *0* none; + faint; ++ moderate; +++ marked

content for the right and left kidneys was 262.3±135.6 (228.6, 106–754.7) mg and 260.2±141.9 (216.5, 89.9-655.8) mg, respectively. Iodine burden measured from combined image using global thresholds for LK and RK are shown in Table 2.

Parameter correlation results

There were good correlations (correlation coefficients 0.62–0.7) between total single kidney iodine (milligrams) and cortical, but not medullary HUs (correlation coefficients 0.22–0.31) with each kidney (Table 3). Cortical versus cortical and medullary versus medullary HUs between kidneys showed high correlations (correlation coefficients 0.86 and 0.75, respectively). There was a statistically significant correlation (r=0.48; P=0.0087) between the number of focal nephrograms in each patient and fluoroscopic procedure time, but not with total contrast used (r=0.28; P=0.14) (Table 4). The qualitative assessments of the global nephrograms showed good to high correlations with cortical and medullary HUs and single kidney total iodine (mg) values (range of correlation coefficients 0.47–0.87) (Table 5).

The baseline eGFRs did not show relationships with either cortical or medullary HUs or single kidney total iodine content. The correlation coefficients ranged from −0.19 to 0.03 and P values ranged from 0.34 to 0.86. There was no statistically significant difference (P=0.4097) in the increase of SCr from baseline in those subjects observed to have global nephrograms.

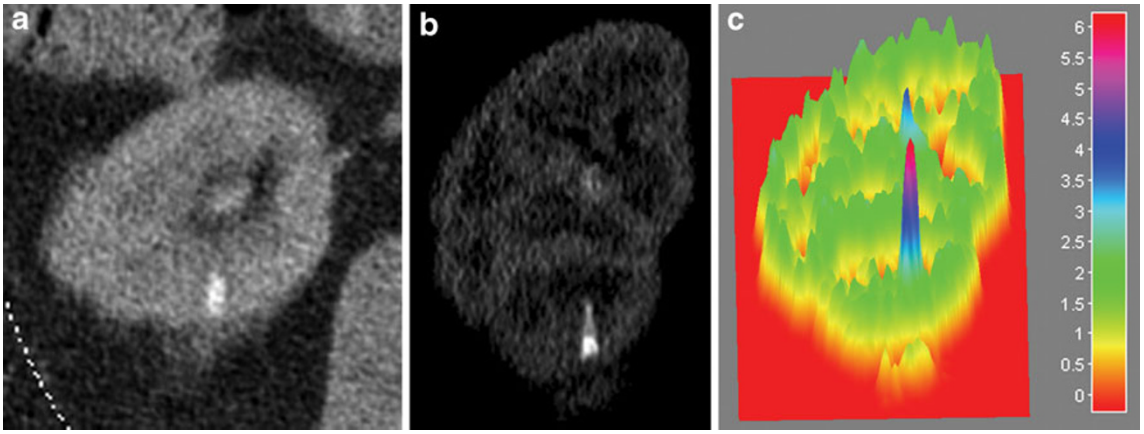

Fig. 3 Non-contrast CT images of a 68-year-old man (patient 12) 24 h after coronary rotational atherectomy and stent requiring a total of 370 ml CM and 32.3 min of fluoroscopy time. **a** Axial image of the right kidney shows a focal nephrogram in the posterior parenchyma superimposed on global nephrograms. **b** Coronal 80-kVp image showing the same focal nephrogram in the lower pole posterior parenchyma. **c** Coronal two-dimensional (2D) colourised graphical image depicting both the global and focal nephrograms. The *colourised scale* on the right aspect of the image is in mgI/ml

There were strong correlations between both CM dose and fluoroscopy time with cortical HUs and single kidney iodine in milligrams, but not medullary HUs (Table 6).

Discussion

We report a frequent occurrence of persistent nephrograms detected by CT 24 h after cardiac catheterisation with or without intervention. Focal nephrograms were observed in 34% (10/29) and bilateral global nephrograms in 45% (13/29) of patients. Positive correlations were found between fluoroscopic procedure time for focal nephrograms and both CM dose and fluoroscopic procedure time for the global nephrograms. There was no correlation between global nephrograms and baseline renal function defined by the eGFR. Increases in SCr at 24–72 h post cardiac catheterisation did not show a relationship to the occurrence of global nephrograms. Four of 29 (14%) of subjects experienced either one or both an increase in SCr≥44 μmol/l (0.5 mg/dl) and ≥25%. These are significant enough transient changes in kidney function to qualify for the criteria defined for CIN [16], although the numbers are too small to establish a direct link to the CM, alone, versus other potential risk factors. No subjects required extended hospitalisation or additional medical management.

Segmental, wedge-shaped nephrograms on delayed imaging studies have been uncommonly reported. Anecdotal case reports were described by Ishikawa et al. [17] in 1985, by Pazimiño et al. [18] in 1983, by Braedel et al. [19] in 1987, and by Trueba-Arguinareña et al. [20] in 1977. Yamazaki et al. [21] reported focal residual contrast media in 16% (17/105) of patients by delayed CT at 24 h following abdominal angiography and found no association with CIN. The focal nephrograms were related to larger volumes of

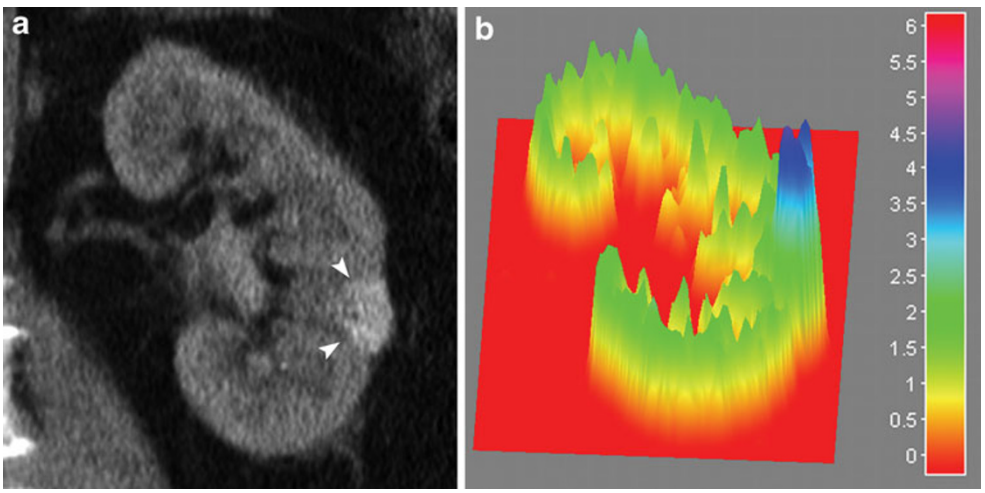

Fig. 4 Non-contrast CT images of a 69-year-old man (patient 14) 24 h after atherectomy and 460 ml CM and 58.6 min of fluoroscopy time. **a** Wedge-shaped focal nephrogram in the coronal image of the left kidney at the 80-kVp CT image. *Arrows* outline the margins of the peripheral, focal nephrogram superimposed on the increased global nephrogram. **b** Coronal 2D colourised graphical depiction of the iodine distribution as shown in Fig. 1c. The colourised scale on the right aspect of the image is in mgI/ml

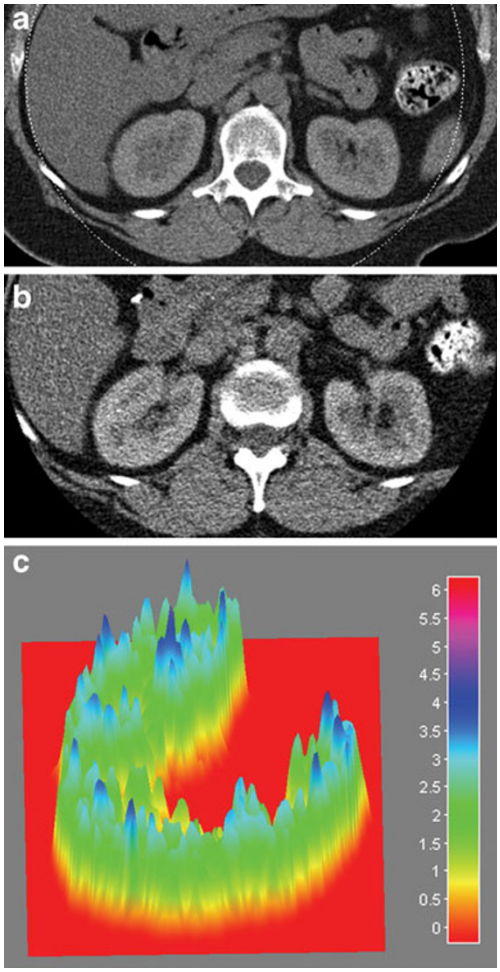

Fig. 5 Non-contrast CT images of a 56-year-old woman (patient 7) 24 h post coronary artery stent placement and utilising 300 ml CM and 20.5 min of fluoroscopy time. **a** Axial combined image shows moderately dense, bilateral nephrograms, cortical regions 71.4 and 65.1 HUs and medullary regions 44.6 and 43.1 HUs, right and left kidneys, respectively. Total iodine 444.04 and 401.17 mg, right and left kidneys respectively. **b** Axial CT images depicted at 80 kVp. **c** Axial 2D colourised graphical image of the right kidney. Vicarious excretion of CM is noted in the colon. The colourised scale on the right aspect of the image is in mgI/ml

contrast media. No specific etiology for these findings was offered.

Monsky et al. [12] described wedge-shaped or linear peripheral nephrograms in 24-h delayed CT scans in 23.3% (14/60) of patients having undergone TACE and found a statistically significant (P=0.029) relationship with procedure time. These authors postulated that these foci represent segmental ischemia and trapped CM in the tubular lumen. Possible etiologies include emboli from either blood or cholesterol plaques from the catheterisation procedure itself.

The well-perfused parenchyma clears the CM, which has a normal biologic half-time of about 1.5 h. However, in the areas with segmental ischemia, the CM does not empty, and

Table 3 Comparison of HU values and single kidney iodine (mg)

Parameters compared	Correlation coefficient	*P* value
RK total I vs		
Cortex HU	0.7	<0.0001
Medullary HU	0.22	0.25
LK total I vs		
Cortex HU	0.62	0.0005
Medullary HU	0.31	0.11
RK vs LK		
Cortex HU	0.86	<0.0001
Medullary HU	0.75	<0.0001
RK vs LK total iodine	0.98	<0.0001

RK right kidney, *LK* left kidney

sodium and water continue to be reabsorbed from the tubular lumen and with a persistence or even an increase in CM concentration. This results in accentuation of the focally ischemic region in comparison with the normal parenchyma (Figs. 2a, b, 3a-c and 4a, b). Cholesterol emboli have been reported to occur in association with angiographic procedures [22, 23]. Furthermore, clots can form around the indwelling catheter. Research has shown that angiographic techniques can lead to the release of particles, presumably made up of bits of clot and fatty plaque material, into the blood. It has also been reported that cholesterol emboli are a known cause of ARF [23].

We do not have a control group of subjects having delayed non-contrast CT scans after CECT, but Jakobsen et al. [24] studied 60 healthy male volunteers by delayed CT at varying doses of iodixanol at four time points up to 5 days after injection. These investigators reported global, but no focal nephrograms.

Prior studies have indicated the observation that micro-emboli occur in the brain and the heart, making it highly likely that renal emboli may likely occur. Büsing et al. [6] prospectively evaluated the incidence of embolic cerebral infarction 12–48 h following diagnostic and interventional coronary angiography in 48 patients using diffusion weighted cerebral MR imaging finding an incidence of 15% (7/48), all of whom were asymptomatic. There was a statistically significant (P=0.017) association with the

Table 4 Comparison of the number of focal nephrograms in each patient and total contrast medium used (mg) and total fluoroscopic time (min)

Parameters compared	Correlation coefficient	*P* value
Total contrast medium vs focal nephrograms	0.28	0.14
Total fluoroscopic time vs focal nephrograms	0.48	0.0087

Table 5 Comparison of Semiquantitative Global Rating Scale vs HU and iodine (mg)

Parameters compared	Correlation coefficient	*p* value
RK cortex HU	0.84	<0.0001
RK medulla HU	0.47	0.01
LK cortex HU	0.87	<0.0001
LK medulla HU	0.57	0.002
RK total I	0.76	<0.0001
LK total I	0.79	<0.0001

RK right kidney, *LK* left kidney

cardiac catheterisation procedure time. They postulated that cerebral emboli associated with catheterisation could be the result of loosened atherosclerotic plaque caused by catheter manipulation, thrombus formation at the catheter, air embolism or, in rare circumstance, foreign material from the catheter or guidewire. The femoral approach was used in all cases.

Lund et al. [7], using multifrequency transcranial Doppler, detected cerebral emboli in 15% of 47 patients undergoing left heart catheterisation. Neuropsychological assessment of 42 of these subjects showed that seven (16.7%) had post catheterisation cognitive impairment.

Myocardial microinfarcts have also been identified after percutaneous coronary intervention [8–10]. Selvanayagam et al. [8] studied 50 subjects after intervention and found that 28% of them had delayed enhancement on cardiac MR images.

We excluded patients with chronic kidney disease (CKD) defined as an eGFR<60 ml/min per 1.73 m^2, subjects [25] who are known to have a much greater risk for AKI following cardiac catheterisation and intervention. This may explain our low rate of AKI as determined by changes in SCr. Further, subjects with CKD require a lesser degree of AKI (change in GFR) to manifest changes in SCr due to the non-linear relationship between GFR and SCr. Changes in the eGFR metric cannot be used to assess AKI, since it established only in steady state CKD subjects [15]. We have not used the term "CIN" in reporting manifestations of AKI as we agree with others that "CIN" presumes causality that may not exist [2, 4, 5, 26].

The diagnosis of AKI related to CIN is usually based on an elevation of SCr of either ≥44 μmol/l (0.5 mg/dl) and/or an increase ≥25% over 24–72 h after the initial insult [16, 27]. However, it is well known that SCr is a poor marker of early renal dysfunction because its concentration is influenced by numerous non-renal factors [5, 28]. It is of even lesser utility in AKI because patients are not in a steady state and substantial rises are not detected until 48–72 h after the initial insult. Significant renal disease can exist with minimal change in SCr because of renal reserve and enhanced tubular secretion of creatinine [29, 30]. On the other hand, significant random SCr fluctuations can occur as "background noise," as pointed out by Newhouse et al. [2]. It is, thus, possible that the nephrographic patterns detected by non-contrast CT are more sensitive indicators of AKI and should be compared with urinary biomarkers, rather than SCr.

The bilateral global nephrographic pattern is possibly less easy to understand. Some previous reports have equated this observation to ARF and CIN [13, 14]. Our review of that literature and the current results of this study do not necessarily document a clear association with either (Table 7). The poor sensitivity of SCr, especially in mild cases of AKI, may be an explanation for the lack of consistently proven association between persistent nephrograms and AKI.

Love et al. [14] proposed a cortical attenuation of 55–110 HU at 24 h to identify patients with subclinical renal impairment and attenuations in excess of 140 HU to be an early indicator of CIN. On the other hand, Jakobsen et al. [24] demonstrated persistence of the cortical nephrogram by sequentially timed delayed CT scans and postulated that retention of CM occurred in the proximal tubular cells and was greater for the nonionic dimer, iodixanol, in comparison with nonionic monomers. The HU levels we have observed and those reported by Yamazaki et al. [11] and Monsky et al. [12] are generally much higher. More than 98% of the iodixanol administered should be excreted within the first 24 h.

It is possible that the persistent global nephrogram is not specific for AKI, but can be a manifestation of significant physiological alteration. Catheter manipulation, intralumi-

Table 6 Comparison of CM and fluoroscopic time vs renal HUs and single kidney iodine (mg)

Parameters compared	Correlation coefficient	*P* value
CM vs		
RK cortex HU	0.8	<0.0001
RK medulla HU	0.3	0.12
LK cortex HU	0.72	<0.0001
LK medulla HU	0.3	0.11
RK iodine (mg)	0.77	<0.0001
LK iodine (mg)	0.74	<0.0001
Fluorotime vs		
RK cortex HU	0.74	<0.0001
RK medulla HU	0.21	0.28
LK cortex HU	0.66	<0.0001
LK medulla HU	0.24	0.21
RK iodine (mg)	0.79	<0.0001
LK iodine (mg)	0.76	<0.0001

RK right kidney, *LRK* left kidney

Table 7 Summary of reports on persistent global nephrograms

Publication	Observations	Change in renal function	Contrast media
Older et al. (1976) [13]	Persistent nephrograms on plain films 24 h after angiography in 17/90 (19%) of patients of which 9/17 (53%) did have and 8/17 (47%) did not have significant change in renal function	↑SCr≥20% or 26.40 μmol/l	HOCM
Love et al. (1989) [14]	Delayed CT cortical enhancement of 141.6 HU 22–26 h after angiography in 1/50 (2%) with any significant change in renal function. Cortical enhancement of 55–110 HU classified as "subclinical renal impairment"	↑SCr=150% of baseline or 88 μmol/l	HOCM and LOCM
Jakobsen et al. (1992) [24]	Cortical attenuation of 52 ± 6 HU at 8–32 h in 40 healthy male volunteers after CECT. No change in renal function. (No focal CT nephrograms reported)	↑SCr, Cr Cl and urinary biomarkers	LOCM, LOCM ionic dimer
Yamazaki et al. (2001) [11]	Delayed CT cortical enhancement 16–21 h after TACE in 81/180 (45%) and nephropathy in 11/180 (6%) of treatments. Minimal cortical retention >50 HU and severe retention >100 HU	↑SCr≥44 μmol/l or ≥25%	HOCM, LOCM, LOCM ionic dimer
Monsky et al. (2009) [12]	CT renal nephrograms 24 h post TACE in 14/60 (23.3%) treatments. Global nephrograms associated with significant (p = 0.031) change in SCr at 24 h. (Delayed segmental nephrograms associated with procedural factors)	↑SCr at 24 h and 24 h from baseline pre-TACE values	IOCM and LOCM

↑*SCr* increase in serum creatinine, *μmol/l* micromol per liter, *CrCl* creatinine clearance, *HOCM* high osmolar contrast media, *LOCM* low osmolar contrast media, *IOCM* iso-osmolar contrast media, *HU* Hounsfield units, *CECT* contrast-enhanced CT, *TACE* transarterial chemoembolisation

nal aortic pressure changes due to bolus injections, temperature changes and CM effects on the endothelium could result in significant stimulation of a richly innervated visceral/endoluminal sympathetic nervous system leading to bilateral renal vasoconstriction [31]. This could lead to stagnation of CM in the tubular lumen and with a prolonged retention time. The medullary region could "flush" the distal tubular CM by persistent and possibly enhanced tubular secretion. This could be an explanation for the unexpected higher cortical than medullary attenuation. Indeed, it has been shown that the tubular secretion of endogenous creatinine increases significantly with ARF and acute glomerular diseases [29, 30, 32]. The expected typical CT nephrographic pattern following a CM i.v. bolus, for example, at 4 ml/s, is an immediate corticomedullary differentiation followed by a homogenous nephrogram.

It might seem a reasonable possibility that the poorer the baseline renal function, the longer the retention of CM. However, we did not observe a statistically significant correlation between baseline eGFR and the presence of the persistent nephrograms. These results suggest, on the other hand, the higher probability of other factors that are procedurally related as a cause.

The strengths of this study include its prospective nature, the comprehensive clinical data, especially a close monitoring of renal function, and the high rates of persistent nephrograms. The latter observations provide a foundation for a potentially rich opportunity for future investigation. The ability to detect focal nephrograms would appear useful to detect the side effects of renal emboli, providing a scoring system for guiding further innovations in cardiac catheterisation techniques. Persistent global nephrograms appear to reflect important alterations in renal physiology. Extreme alterations, especially in more vulnerable subjects with renal insufficiency could then manifest as AKI.

Weaknesses in this study include the small patient population. However, this is a pilot study and, as noted above, the findings of persistent nephrograms have been observed to be at surprisingly high rates. Only four subjects manifested significant changes in renal function as measured by their SCr. Thus, no firm conclusions can be made about any specific risk factors or relationships to CIN. The major risk factor for CIN is pre-existing renal insufficiency which was not an enrollment criterion in this study. Also, and as emphasised by Newhouse et al. [2], one must be cautious not to attribute all cases of AKI to the CM, per se, in order to avoid the post hoc, ergo propter hoc logical fallacy. Future studies will expand enrollment to include these subjects.

We did not acquire pre-cardiac catheterisation CT scans as baseline and we may have overestimated the occurrence of global nephrograms. However, we derived our subjective nephrogram ratings regarding this aspect of the study from our previous work where we did have access to this information, as reported by Monsky et al. [12]. Also, the delayed renal attenuation, we observed and defined as positive nephrograms, is similar to that reported and summarised in Table 7. It is unlikely that we have overestimated the focal nephrogram findings since no patient was enrolled if they had had CM with 72 h of their cardiac catheterisation procedure.

Dual-energy scan data were inadvertently lost in 11/29 patients. We used a methodology described in the "Electronic supplementary material" section that employed

a novel technique of training sets derived from the data on the successfully acquired dual-energy data sets. We believe iodine quantification is a valuable approach, noting high correlation coefficients between our total renal iodine determinations and right and left kidneys, cortical HUs, global nephrograms, CM dose and fluoroscopic procedure times.

We estimate an additional radiation dose of approximately 3.4 mSv for these CT scans, which is another negative aspect of our study. However, the incremental dose compared with the cardiac catheterisation procedure is small, the images are limited to the kidneys, and can be rapidly performed.

In conclusion, delayed CT nephrograms post cardiac catheterisation and intervention manifest a high positive occurrence of both segmental and global nephrograms. These findings correlate with procedural factors such as fluoroscopic time and total amount of contrast medium utilised. Our data, and what has been previously reported, are yet too limited to prove a relationship between the global nephrogram and CIN.

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