Iodinated Contrast and Acute Kidney Injury: Major Culprit or Innocent Bystander? Time for Reappraisal*

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Contrast-induced nephropathy (CIN) is a major cause of hospital-acquired acute kidney injury (AKI). Its prevalence is highly variable, which is linked to the studied populations' baseline characteristics and comorbidities and to the lack of uniformity in definitions used (1). The overall prevalence is estimated between 1% and 30% of patients receiving iodinated contrast medium (CM). Decreased baseline glomerular filtration rate, diabetes, heart failure, hypotension, dehydration, and older age, with the type and amount of CM, are the main recognized risk factors.

Patients in the ICU have frequently multiple, often unavoidable, AKI risk factors (sepsis, shock, and nephrotoxic medications), undergo the growing use of imaging and interventional procedures (2), and are more and more older (3). Thus, they seem particularly exposed to CIN.

Until very recently, data on CIN in ICU patients were rather scarce. In two retrospective studies, the prevalence has been evaluated at 16.3% in surgical ICU patients and at 14% in medical ones (4, 5). The prevalence was 19% in a prospective study among surgical patients (6). Because of the usual multifactorial origin of AKI in the ICU, no conclusion concerning the relationship between CM infusion and renal function impairment can be drawn from these studies. With the exception of one small sample study (where CIN prevalence was very low, and its definition very different from the usually accepted ones) (7), no results comparing the prevalence of AKI in the presence or absence of CM infusion in ICU patients have been published.

That is precisely what Ehrmann et al (8) did in their study published in this issue of *Critical Care Medicine*. The authors assessed the prevalence and mortality of monomeric nonionic low-osmolar CM-associated AKI in two ICUs. They studied prospectively a cohort of 380 patients (with a large case mix including medical, trauma, and surgical ones) composed by 307 expositions to CM and 170 control expositions (imaging without CM or intrahospital transport). Their main result was that the use of monomeric nonionic low-osmolar CM agents did not affect the prevalence of AKI nor the hospital mortality.

Indeed, some limits apply to this work.

First, definitive conclusion can be drawn from the mortality analysis, and data concerning long-term outcomes are lacking.

Second, control inclusions were largely represented by patients who underwent imaging procedures without CM infusion. Among them, it cannot be excluded that the decision not to use CM may be linked to a presumed high risk of CIN. Furthermore, increase in serum creatinine concentration has already been described in noncritically ill patients who had CT scan without CM administration (9).

Finally, large proportion of patients treated with one or more nephrotoxic medications (excluding CM) may have contributed to dilute the specific role of CM in the occurrence AKI.

The direct role of CM in AKI in critically ill patients remains unclear. Further prospective studies on CIN, using a consensual definition (as done for AKI of other causes) for the sake of clarity and uniformity, are needed. Until more results become available, the exact role of CM, ranging from major culprit to innocent bystander, will remain questionable.

*See also p. 1017.

Key Words: acute kidney injury; contrast-induced nephropathy; nonionic low-osmolar

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Acute Kidney Injury in the Critically Ill: Is Iodinated Contrast Medium Really Harmful?*

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Objectives: To assess whether the use of iodinated contrast medium increases the incidence of acute kidney injury in ICU patients, compared with patients not receiving iodinated contrast medium.

Design: Prospective observational matched cohort study.

Setting: Two ICUs in two tertiary teaching hospitals.

Patients: A total of 380 adults were included (20% more than once), before an iodinated contrast medium infusion (contrast inclusions, $n = 307$) or before an intrahospital transfer without iodinated contrast medium infusion (control inclusions, $n = 170$).

Interventions: None.

Measurements and Main Results: Among contrast inclusions, iodinated contrast medium–associated acute kidney injury occurred after 23 administrations (7.5%) according to the Acute Kidney Injury Network definition (stage ≥ 1, over 48 hr). As expected, a broader definition (≥ 25% increase in serum creatinine over 72 hr) yielded a greater incidence (16%). In 146 pairs of contrast and control inclusions, matched on propensity for iodinated contrast medium infusion, the incidence of acute kidney injury was similar (absolute difference in incidence, 0%; 95% confidence interval, −5.2; 5.2%), Acute Kidney Injury Network definition). Hospital mortality was also similar in 71 contrast and 71 control patients included only once and matched the same way. Contrary to iodinated contrast medium infusion (odds ratio, 1.57; 95% confidence interval, 0.69–3.53), the Sequential Organ Failure Assessment score at inclusion (odds ratio, 1.18; 95% confidence interval, 1.07–1.31) and the number of other nephrotoxic agents (odds ratio, 1.38; 95% confidence interval, 1.03–1.85) were independent risk factors for acute kidney injury.

Conclusions: The specific toxic effect of monomeric nonionic low-osmolar iodinated contrast medium in ICU patients with multiple renal aggressions seemed minimal. Severity of disease and the global nephrotoxic burden were risk factors for acute kidney injury, regardless of iodinated contrast medium infusion. (*Crit Care Med* 2013; 41:1017–1026)

Key Words: contrast medium/adverse effects; intensive care units; kidney diseases/chemically induced; kidney disease/epidemiology; tomography/x-ray computed

Iodinated contrast medium (CM)-associated acute kidney injury (CA-AKI) is a frequent cause of hospital-acquired kidney dysfunction (1). Aside from direct tubular toxicity of CM, mechanisms of CA-AKI involve modified blood rheology, renal vasoconstriction, and production of reactive oxygen species leading to both compromised renal oxygen supply and oxidative stress (2). Of note, during systemic inflammatory response from various causes (sepsis, shock, trauma, etc.), these biological processes are also important contributors to organ injury and failure (including the kid-

*See also p. 1149.

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Drs. Ehrmann, Pajot, and Lakhal were involved in conception and design. Drs. Ehrmann, Badin, Savath, and Lakhal helped in patient recruitment and inclusions. Drs. Ehrmann and Pham were involved in data analysis. Dr. Ehrmann, Dr. Badin, Dr. Savath, Dr. Pajot, Dr. Garot, Dr. Pham, Prof. Capdevila, Prof. Perrotin, and Dr. Lakhal were involved in manuscript preparation/revision.

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ney) observed in ICU patients (3–6). Furthermore, the use of nephrotoxic agents other than CM is common in the ICU (7). Thus, on the one hand, critically ill patients may be particularly prone to develop CA-AKI through worsening of an ongoing renal injury (prior to CM infusion). On the other hand, the specific additional toxicity of CM may be clinically negligible within this context of overwhelming inflammation, compromised oxygen transport, and renal toxic agents. Indeed, some authors consider that the risk of CA-AKI is overrated and may be considered clinically insignificant when weighed against the diagnostic benefit of CM (8, 9).

Compared with patients undergoing coronary angiography, relatively few studies addressed CA-AKI in ICU patients. Most of them were retrospective (10–15), in single center settings (10, 12, 14–18), in specific populations (12, 16, 18), of limited sample size (13, 15–19), and importantly, did not include a control group (10, 11, 13, 14, 16–18).

The aim of this prospective study was to assess whether the use of CM increases the incidence of AKI in ICU patients to an important extent or in a clinically negligible manner, compared with patients not receiving CM.

MATERIALS AND METHODS

This observational study was approved by the regional ethics review board (Comité de Protection des Personnes, Tours, France) who waived the need for informed consent.

All patients admitted to one of the two participating ICUs (Center 1: surgical and trauma-oriented ICU; Center 2: medical-oriented ICU) between March 1, 2008, and March 31, 2009, were prospectively included if they underwent: 1) a parenteral CM infusion during their ICU stay or within the day before ICU admission (contrast inclusion) or 2) an intrahospital transfer, during their ICU stay, without parenteral CM infusion (control inclusion). Imaging procedures without parenteral CM within the day before ICU admission were also considered control inclusions. Patients were not included in cases of ICU length of stay less than 48 hours, renal replacement therapy within the previous week, and lack of serum creatinine measurement in the 24 hours before to 6 hours after inclusion or in the subsequent 96 hours. Patients meeting inclusion criteria more than once were included each time they were eligible.

All serum creatinine measurements sampled 24 hours before to 96 hours after inclusion were recorded. AKI was defined as stage ≥1 of the Acute Kidney Injury Network (AKIN) classification (≥26.4 μmol/L or ≥50% increase of serum creatinine) or according to the common definitions (≥ 44 μmol/L, ≥25% increase in serum creatinine) over 48, 72, and 96 hours after inclusion (1, 10, 11, 13–17, 20). When not specified otherwise, AKIN definition over 48 hours was used. *AKI* refers to injury occurring indistinctively after contrast and control inclusion, whereas *CA-AKI* specifically refers to injury occurring after contrast inclusion. Clinical and demographic data were collected (**Tables 1** and **2**) as well as nephrotoxic agents administered 24 hours before to 48 hours after inclusion (**Supplemental Table E1**, Supplemental Digital Content 1, http://links.lww.com/CCM/A569).

TABLE 1. Patient Characteristics

Characteristics	Mean ± SD or Count (%)
Age (yr)	56 ± 19
Female	139 (37%)
Simplified Acute Physiology Score II at ICU admission	41 ± 16
ICU length of stay (d)	18 ± 18
ICU mortality	59 (15%)
Hospital length of stay after ICU admission (d)	31 ± 27
Hospital mortality	82 (24%)
Comorbidities	
Hypertension	140 (37%)
Diabetes mellitus	53 (14%)
Chronic kidney failure	28 (7%)
Chronic heart failure	8 (2%)
Baseline serum creatinine (μmol/L)	78 ± 35
Main diagnosis at ICU admission	
Acute respiratory failure	102 (27%)
Coma	95 (25%)
Trauma	74 (20%)
Shock	53 (14%)
Postoperative	33 (9%)
Cardiac arrest	14 (4%)
Acute renal failure	2 (0.5%)
Other	6 (2%)
Sepsis at admission	137 (36%)
Type of admission	
Medical	290 (76%)
Emergency surgery	85 (22%)
Scheduled surgery	5 (1%)

Hypertension, diabetes mellitus: requiring pharmacological therapy. Chronic kidney failure: baseline creatinine clearance < 60 mL/min/1.73 m^2. Chronic heart failure: New York Heart Association dyspnea stage III or IV. Baseline serum creatinine was recorded within the last year (outside any acute change of kidney function). Type of admission was categorized according to the Simplified Acute Physiology Score II.

Statistical Analysis

Between-group comparisons relied on Student *t*, chi-square, or Fisher exact tests, as appropriate. Paired comparisons were based on the McNemar and Wilcoxon rank sum tests. To compare AKI incidences, contrast and control inclusions were matched (without replacement) on their propensity for CM infusion to mimic randomization to a certain extent in an observational study de-

TABLE 2. Characteristics at Inclusion

	Overall	contrast Inclusions	control Inclusions	
	n = 477	*n* = 307	*n* = 170	*p*
Days between admission and inclusion	5 ± 9	4 ± 8	7 ± 9	< 0.01
Serum creatinine (μmol/L)	95 ± 58	93 ± 54	99 ± 65	0.28
Sequential Organ Failure Assessment score	4.8 ± 3.2	4.6 ± 3.3	5.0 ± 3.0	0.19
Mechanical ventilation				
Invasive/noninvasive	323 (68%)/11 (2%)	191 (62%)/3 (1%)	132 (78%)/8 (5%)	< 0.01
Pao_2/Fio_2 (mm Hg)	274 ± 122	268 ± 123	282 ± 119	0.28
Positive end-expiratory pressure (cm H_2O)	5 ± 2	5 ± 3	5 ± 2	0.43
Mean arterial pressure (mm Hg)	84 ± 19	83 ± 20	87 ± 17	0.02
Arterial lactate (mmol/L)	2.0 ± 2.0	2.1 ± 2.2	1.6 ± 1.6	< 0.01
Hemoglobin concentration (g/dL)	11.0 ± 2.5	11.1 ± 2.6	10.9 ± 2.2	0.51
Catecholamines	81 (17%)	58 (19%)	23 (13%)	0.13
Epinephrine (μg/kg/min)	0.2 ± 0.1 [*n* = 4]	0.2 ± 0.1 [*n* = 4]	*n* = 0	NA
Dobutamine (μg/kg/min)	3.7 ± 2.5 [*n* = 7]	3.6 ± 1.8 [*n* = 5]	3.9 ± 5.1 [*n* = 2]	0.95
Dopamine (μg/kg/min)	7.3 ± 2.5 [*n* = 3]	7.3 ± 2.5 [*n* = 3]	*n* = 0	NA
Norepinephrine (μg/kg/min)	0.3 ± 0.3 [*n* = 73]	0.3 ± 0.3 [*n* = 52]	0.2 ± 0.4 [*n* = 21]	0.32
Acute circulatory failure[a]	213 (45%)	154 (50%)	59 (35%)	< 0.01
Infection[b]	197 (41%)	136 (44%)	61 (36%)	0.07
Fluid loading (mL)[c]	2782 ± 2662 [*n* = 319]	3166 ± 2994 [*n* = 213]	2010 ± 1568 [*n* = 106]	< 0.01
Fluid balance (mL)[d]	1398 ± 2231	1574 ± 2461	1081 ± 1704	0.02
Nephrotoxic agents ≥1 (excluding iodinated contrast medium)[e]	317 (66%)	199 (65%)	118 (69%)	0.31
Increase in serum creatinine after inclusion (μmol/L)				
48 hr	0.9 ± 32	2.7 ± 31	−2.4 ± 33	0.1
72 hr	3.6 ± 37	5.7 ± 38	−0.2 ± 35	0.09
96 hr	5.1 ± 41	7.3 ± 43	1.3 ± 36	0.13
Time of inclusion				
Imaging the day before admission	48 (10%)	38 (12%)	10 (6%)	0.13
Imaging during ICU stay	400 (84%)	269 (88%)	131 (77%)	
Intrahospital transfer without imaging	29 (6%)		29 (17%)	

NA = not applicable.

[a]Acute circulatory failure: catecholamine infusion or mean arterial pressure <65 mm Hg or arterial lactate >2 mmol/L.

[b]Infection: new curative antibiotic treatment or positive blood culture within 48 hr before inclusion.

[c]Fluid loading: infusion of osmotically active fluids (crystalloids, colloids, and blood products) excluding baseline hydration within 12 hr before/after inclusion.

[d]Fluid balance: difference between all fluid input and output within 12 hr before/after inclusion.

[e]At least one other nephrotoxic agent within 24 hr before to 48 hr after inclusion. Details about nephrotoxic agents are provided in the supplemental data, Supplemental Digital Content 1, http://links.lww.com/CCM/A569. Values are indicated as mean ± SD and count (%). *p* values correspond to comparison of contrast and control inclusions.

sign. For each inclusion, the propensity score for CM infusion was calculated through logistic regression, including clinically plausible variables associated with CM infusion in univariate analysis ($p < 0.1$) (**Supplemental Figure E1**, Supplemental Digital Content 1, http://links.lww.com/CCM/A569). Contrast and control inclusions were matched if their propensity score was similar (i.e., difference below 0.2 × SD of the logit of the propensity score) (21).

Risk factors for AKI and CA-AKI were assessed using backward sequential logistic regression; clinically plausible variables associated with AKI in the univariate analysis ($p < 0.1$) were entered in the initial model which was then simplified (22). As significant differences in case mix appeared between the two participating centers (**Supplemental Table E2**, Supplemental Digital Content 1, http://links.lww.com/CCM/A569), center was introduced in all multivariate analyses. Logit linearity of continuous variables was assessed graphically (22). To assess the association between CM infusion and the risk of subsequent AKI, the type of inclusion (contrast or control) was forced into the final logistic regression model of AKI risk factors.

The impact of AKI on hospital mortality was assessed in the subset of patients included only once (contrast and control pairs matched on the propensity for CM infusion, as described; **Supplemental Fig. E2**, Supplemental Digital Content 1, http://links.lww.com/CCM/A569).

Based on retrospective data (10), we determined that with an alpha risk of 5% and a power of 80%, one would need to compare 2×132 inclusions to significantly detect an AKI incidence twice as high in the contrast group compared with the control group (23% vs. 11.5% with the most sensitive CA-AKI definition). Indeed, given the diagnostic benefit associated with CM infusion, only a large difference in AKI incidence between contrast and control inclusions would lead clinicians to refrain from administering CM. Thus, we empirically planned to perform at least 450 inclusions.

Data were collected using Filemaker Pro (Filemaker Inc., Santa Clara, CA), and statistical calculations were performed with SPSS 16.0 (SPSS, Chicago, IL) and R (R Foundation for Statistical Computing, Vienna, Austria). Unless specified, data were reported as mean ± SD or count (%). All statistical tests were two tailed, and a p value less than 0.05 was considered significant.

RESULTS

Patients and Inclusions

In 380 patients, 477 inclusions were analyzed (**Fig. 1** and Table 1). Seventy-five patients (20%) were included more than once (**Supplemental Table E3**, Supplemental Digital Content 1, http://links.lww.com/CCM/A569). contrast ($n = 307$) and control ($n = 170$) inclusions were similar except for some aspects detailed in Table 2.

A median of 7 (25th–75th percentile: 6–8) measurements of serum creatinine *per* inclusion were available over the 96-hour observation period. All CM were monomeric nonionic low-osmolar agents (volume 112 ± 30 mL, intravenous in 280 [91%] inclusions,

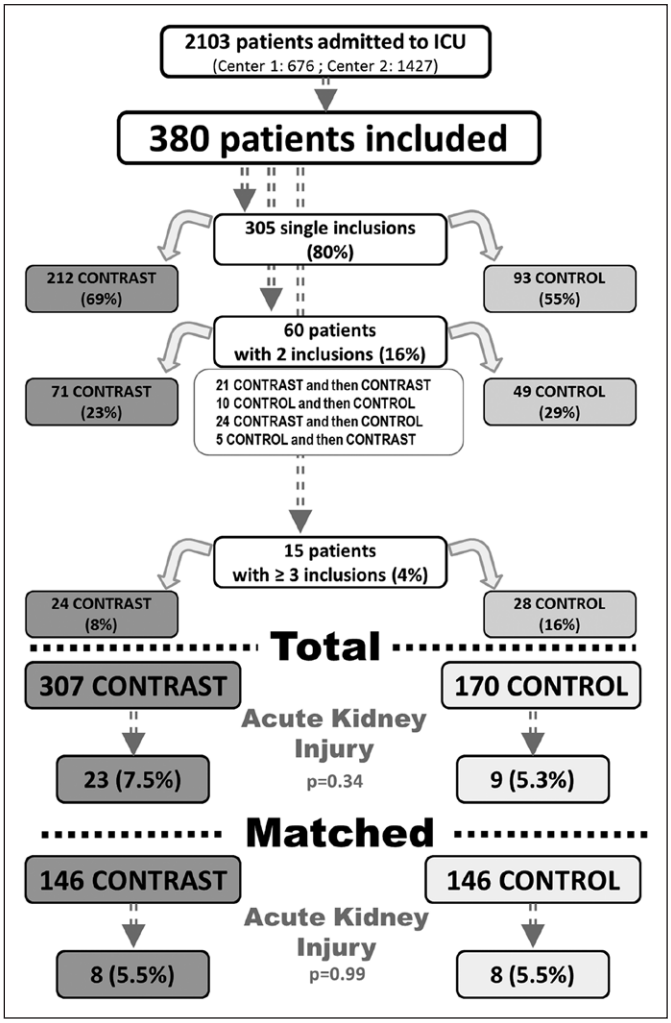

Figure 1. Study flow chart. Acute kidney injury is defined according to the Acute Kidney Injury Network stage ≥1 criterion over 48 hr (see text for details). Contrast denotes patients included after parenteral iodinated contrast medium infusion 24 hr before or during the ICU stay. Control denotes patients included after intrahospital transfer without parenteral iodinated contrast medium infusion while in the ICU or imaging procedures without parenteral iodinated contrast medium infusion 24 hr before ICU admission. Data are indicated as count (%).

iohexol; $n = 167$ [54%]/iomeprol $n = 103$ [34%]/iobitridol $n = 19$ [6%]/ioversol $n = 15$ [5%]/iopamidol $n = 3$ [1%]). The use of nephroprotective agents (N-acetylcysteine or sodium bicarbonate) was infrequent (6% of contrast inclusions, **Table 3**).

Incidence of AKI

In contrast inclusions, the incidence of CA-AKI ranged from 4% to 17%, depending on the definition (**Fig. 2**). In crude (unmatched) comparison of contrast and control inclusions, incidence of AKI was higher in contrast inclusions, but not significantly, whatever the definition used for AKI (Fig. 2).

Among 307 contrast inclusions, 146 could be matched with 146 control inclusions with respect to their propensity for CM infusion (Supplemental Fig. E1, Supplemental Digital Content 1, http://links.lww.com/CCM/A569). Over the 96-hour observation period, their respective serum

TABLE 3. Contrast Inclusions and Iodinated Contrast Medium–Associated Acute Kidney Injury

	CA-AKI	No CA-AKI	
	n = 23	*n* = 281	*p*
Simplified Acute Physiologic Score II at ICU admission	47 ± 19	40 ± 15	0.048
Type of admission			
Medical	16 (69%)	202 (72%)	0.86
Emergency surgery	7 (30%)	75 (27%)	
Scheduled surgery	0	4 (1%)	
Comorbidities			
Hypertension[a]	8 (35%)	90 (21%)	0.79
Diabetes mellitus[a]	2 (9%)	34 (12%)	0.99
Cirrhosis[b]	2 (9%)	3 (1%)	0.048
Chronic kidney failure[c]	4 (17%)	13 (5%)	0.03
Chronic heart failure[d]	0 (0%)	4 (1%)	0.99
Baseline serum creatinine (μmol/L)[e]	82 ± 29	74 ± 27	0.22
Change in serum creatinine 48 hr before inclusion			
Absolute (μmol/L)	7 ± 39	−2 ± 21	0.28
Relative (%)	11 ± 33	−1 ± 19	0.09
Serum creatinine at inclusion	118 ± 55	91 ± 53	0.02
Change in serum creatinine after inclusion (μmol/L)			
48 hr	77 ± 65	−3.4 ± 15	< 0.01
72 hr	86 ± 89	−0.7 ± 20	< 0.01
96 hr	91 ± 113	0.5 ± 21	< 0.01
Sequential Organ Failure Assessment score at inclusion	6.8 ± 3.9	4.4 ± 3.1	< 0.01
Acute circulatory failure at inclusion	20 (87%)	133 (47%)	< 0.01
Infection at inclusion[f]	11 (48%)	124 (44%)	0.73
Arterial lactate at inclusion (mmol/L)	3.6 ± 3.3	2.0 ± 2.0	0.04
Mean arterial pressure at inclusion (mm Hg)	80 ± 21	83 ± 20	0.50
Catecholamines at inclusion	6 (26%)	52 (18%)	0.41
Epinephrine (μg/kg/min)	0.2 [*n* = 1]	0.2 ± 0.2 [*n* = 3]	0.99
Dobutamine (μg/kg/min)	*n* = 0	3.6 ± 1.8 [*n* = 5]	NA
Dopamine (μg/kg/min)	*n* = 0	7.3 ± 2.5 [*n* = 3]	NA
Norepinephrine (μg/kg/min)	0.3 ± 0.3 [*n* = 6]	0.3 ± 0.3 [*n* = 46]	0.83
Fluid loading (mL)[g]	4602 ± 3241 [*n* = 20]	3017 ± 2936 [*n* = 193]	0.02
Fluid balance (mL)[h]	2939 ± 2601	1491 ± 2440	0.02
Mechanical ventilation at inclusion (invasive/noninvasive)	17 (74%)/0	172 (61%)/3 (1%)	0.50
Pao_2/Fio_2 (mm Hg)	230 ± 140	271 ± 122	0.19
Positive end-expiratory pressure (cm H_2O)	5 ± 3	5 ± 2	0.99

(Continued)

TABLE 3. (*Continued*). Contrast Inclusions and Iodinated Contrast Medium–Associated Acute Kidney Injury

	CA-AKI	No CA-AKI	
	n = 23	*n* = 281	*p*
Contrast medium			
Route of infusion (arterial/venous)	4 (17%)/19 (83%)	23 (8%)/258 (92%)	0.13
Volume (mL)	126 ± 54	112 ± 27	0.20
Iohexol	12 (52%)	153 (54%)	
Iomeprol	8 (35%)	95 (34%)	
Iobitridol	0	18 (6%)	
Ioversol	3 (13%)	12 (4%)	
Iopamidol	0	3 (1%)	0.32
Imaging location			
Thorax	17 (74%)	169 (60%)	0.19
Abdomen and pelvis	15 (65%)	158 (56%)	0.40
Brain	13 (56%)	121 (43%)	0.21
Spine	8 (35%)	39 (14%)	0.01
Soft tissues	2 (9%)	17 (6%)	0.64
Time of inclusion			0.83
24 hr before ICU admission	4 (17%)	34 (12%)	
Day of ICU admission	1 (4%)	16 (6%)	
During ICU stay (5 ± 9 d after admission)	18 (78%)	231 (82%)	
Number of nephrotoxic agents (excluding contrast medium)			
0	3 (13%)	103 (37%)	0.01
1	4 (17%)	78 (28%)	
2	11 (48%)	65 (23%)	
≥ 3	5 (22%)	35 (12%)	
Nephrotoxic agents ≥ 1 (excluding contrast medium)[i]	20 (87%)	178 (63%)	0.02
Nephroprotective agents[j]	0 (0%)	18 (6%)	0.38

CA-AKI = contrast medium associated acute kidney injury; NA = not applicable.

CA-AKI defined as Acute Kidney Injury Network stage ≥1 (see text for details) within 48 hr of contrast medium infusion (as three inclusions lacked serum creatinine within 48 hr after inclusion, only 304 inclusions are presented). Type of admission was categorized according to the Simplified Acute Physiology Score II.

[a]Hypertension, diabetes mellitus: requiring pharmacological therapy.

[b]Cirrhosis: pathology documented or obvious portal hypertension.

[c]Baseline serum creatinine was recorded within the last year (outside any acute change of kidney function).

[d]Chronic kidney failure: baseline creatinine clearance < 60 mL/min/1.73 m^2.

[e]Acute circulatory failure: catecholamine infusion or mean arterial pressure <65 mm Hg or arterial lactate >2 mmol/L.

[f]Infection: new curative antibiotic treatment or positive blood culture within 48 hr before inclusion.

[g]Fluid loading: infusion of osmotically active fluids (crystalloids, colloids, and blood products) excluding baseline hydration within 12 hr before/after inclusion.

[h]Fluid balance: difference between all fluid input and output within 12 hr before/after inclusion. Values are indicated as mean ± sd and count (%). *p* values correspond to comparison of inclusion experiencing or not CA-AKI.

[i]Details about nephrotoxic agents are provided in the supplemental data, Supplemental Digital Content 1, http://links.lww.com/CCM/A569.

[j]At least one administration of N-acetylcystine or sodium bicarbonate 24 hr before to 48 hr after contrast medium inclusion.

creatinine changes were 7.8 ± 51 μmol/L and 0.5 ± 38 μmol/L ($p = 0.78$). As for crude comparison, AKI incidence did not significantly differ between contrast and control matched inclusions, whatever the definition (**Fig. 3**). For the most sensitive definition of AKI (25% increase in serum creatinine over 96 hr), the respective incidences were 16.4% and 12.3% (absolute difference, 4.1%; 95% confidence interval [95% CI], –4.6; 12.1%).

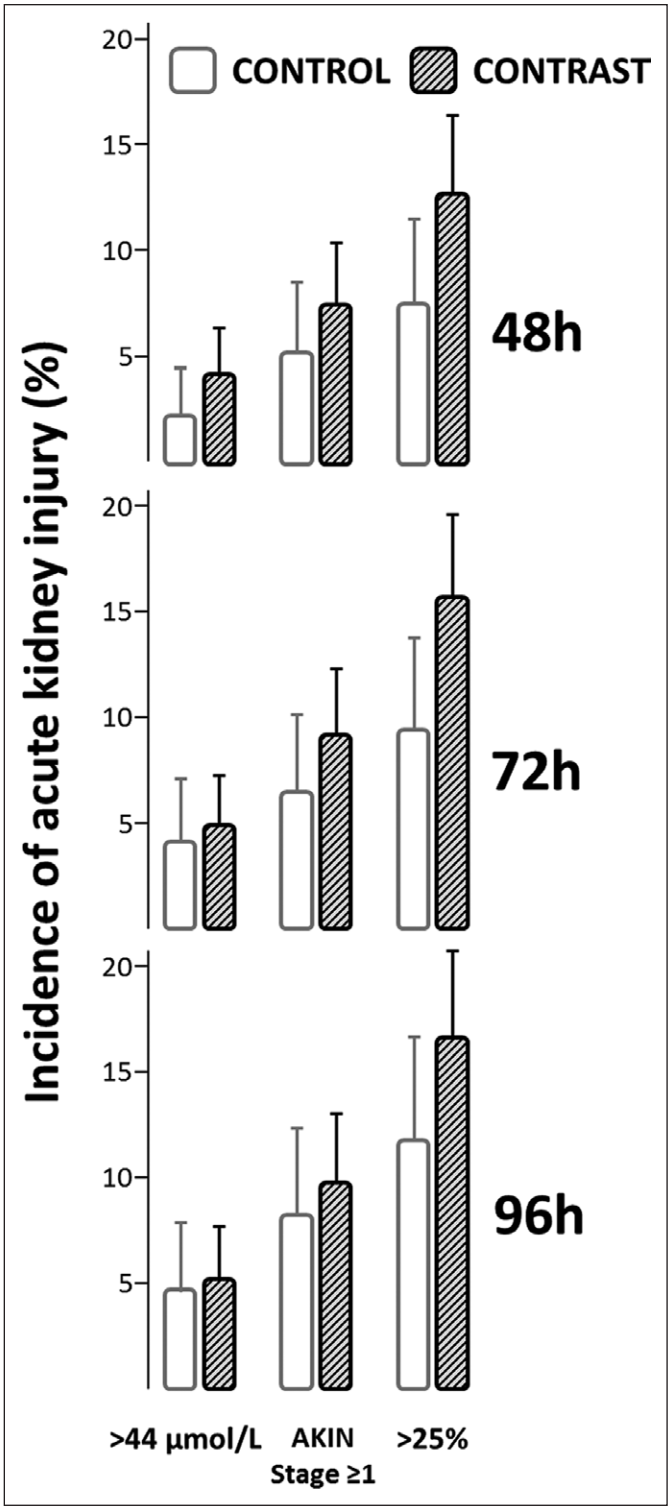

Figure 2. Incidences of acute kidney injury (AKI) in the whole population. AKI was defined according to three definitions: ≥ 44 µmol/L and ≥ 25% increase in serum creatinine, Acute Kidney Injury Network (AKIN) stage ≥1 criterion (see text for details) over three time frames: 48, 72, and 96 hr after inclusion. Data are represented as percentage, error bars represent 95% confidence intervals. Comparisons of incidences between contrast and control inclusions were nonsignificant for all definitions ($p > 0.05$).

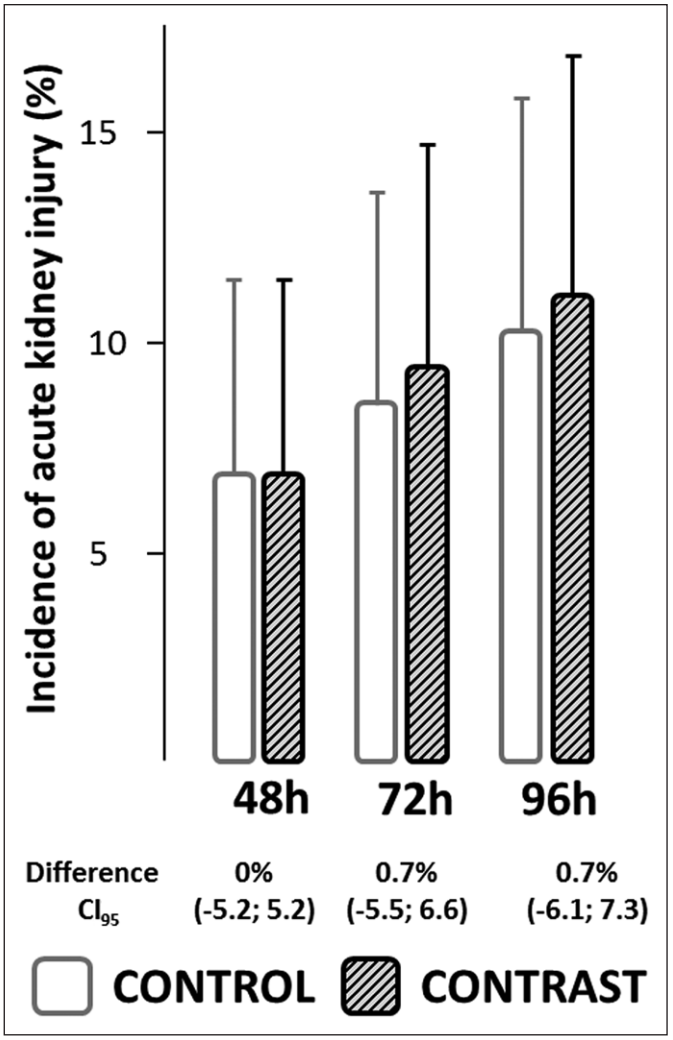

Figure 3. Incidences of acute kidney injury (AKI) in matched contrast and control inclusions. AKI was defined according to the Acute Kidney Injury Network stage ≥1 criterion over 48, 72, and 96 hr (see text for details). Data are represented as percentage, error bars represent 95% confidence intervals (CI_{95}). Paired comparisons of incidences between the 146 contrast and 146 control inclusions were nonsignificant ($p > 0.05$).

Risk Factors for AKI

Among risk factors listed in Table 3, multivariate analysis revealed the Sequential Organ Failure Assessment (SOFA) score (23) at inclusion (odds ratio, 1.19; 95 CI%, 1.05–1.34) and the number of nephrotoxic agents (excluding CM) administered 24 hours before to 48 hours after inclusion (odds ratio, 1.47; 95 CI%, 1.03–2.11) as independent risk factors for CA-AKI (**Supplemental Table E4**, Supplemental Digital Content 1, http://links.lww.com/CCM/A569). In the whole population, CM infusion (odds ratio, 1.57; 95% CI, 0.69–3.53; $p = 0.30$) was not independently associated with AKI (**Table 4**). When considering CM as part of the nephrotoxic burden, the latter was independently associated with AKI (**Supplemental Fig. E3** and **Table E5**, Supplemental Digital Content 1, http://links.lww.com/CCM/A569).

TABLE 4. Logistic Regression Model Predicting Acute Kidney Injury in Contrast and Control Inclusions

	Odds Ratio	95% Confidence Interval	*p*
Center	1.57	0.68–3.65	0.29
Sequential Organ Failure Assessment score	1.18	1.07–1.31	< 0.01
Number of nephrotoxic agents (excluding iodinated contrast medium)	1.38	1.03–1.85	0.03
Contrast medium infusion	1.57	0.69–3.53	0.30

Goodness of fit (Hosmer-Lemeshow): $\chi^2 = 7.484$, $p = 0.485$ (8 *df*).

Area under the receiver operating characteristics curve: 0.72 (0.63–0.80).

Odds ratios were computed for the dependent variable "Acute kidney injury" defined per Acute Kidney Injury Network stage ≥ 1 criterion within 48 hr after inclusion (see text for details) and unit increases in independent variables. Reference category for center variable is center 1. Other nephrotoxic agents excluding contrast medium were recorded 24 hr before to 48 hr after contract medium infusion (Supplemental Table E1, Supplemental Digital Content 1, http://links.lww.com/CCM/A569) and were coded into four categories (0, 1, 2, and 3 or more nephrotoxic agents).

Impact on Outcome

Renal Replacement Therapy. As expected, when AKI developed (whatever the definition), the incidence of renal replacement therapy (within 7 days) was significantly higher than in inclusions not experiencing AKI (6 [18.8%] vs. 6 [1.4%]) ($p < 0.01$).

In the 146 contrast/control matched inclusions, the incidence of renal replacement therapy was similar (2.1% and 2.8%, respectively; $p > 0.05$; absolute difference, 0.7%; 95% CI, –3.03%;3.85%).

Mortality. Overall, in crude analysis of patients included only once ($n = 305$), hospital mortality was significantly higher in patients developing AKI (44% vs. 23%; $p = 0.02$, AKIN 96 hr definition). On their propensity for CM infusion, 71 contrast inclusions (among 212) were matched with 71 control inclusions (among 93) (Supplemental Fig. E2, Supplemental Digital Content, http://links.lww.com/CCM/A569), and similar hospital mortalities were observed in the two groups: 22 (31%) vs. 20 (28%), respectively; $p = 0.85$, absolute difference, 3%; 95% CI, –13%;19%).

DISCUSSION

The main finding of this prospective bicentric study with a large case mix, including medical, trauma, and surgical patients is that the use of monomeric nonionic low-osmolar CM agents did not significantly affect the incidence of AKI. Hence, the specific toxic effect of these CM seemed minimal in our population mainly exposed to intravenous (rather than intra-arterial) CM and receiving numerous other nephrotoxic agents.

Incidence of CA-AKI

Our results are consistent with recent retrospective studies in the ICU setting. In the largest one, Hoste et al (11) recently reported the same incidence of 16% we observed with the same definition. With consistent definitions and considering similar inclusion criteria, several authors also found a similar incidence to that observed in our study (11–13, 15, 16, 18), whereas different incidence were reported elsewhere (10, 14, 17). Altogether, one may consider that CA-AKI incidence is about 5% to 20% when using a modern definition, such as the AKIN classification. Differences in case mix and in AKI risk factors prevalence may explain the observed variability across studies.

Specific Impact of CM on Kidney Function and Patients' Outcome

We observed no significant difference in AKI incidence between matched contrast and control inclusions. In ICU patients, a similar observation was made by Ng et al (12) but the limited sample size, the retrospective design, and the specific context of an oncologic ICU may have downplayed generalizability of their findings. Our prospective study confirms, in a larger number of inclusions (including trauma and emergency surgery patients), that the impact of modern CM on AKI incidence seems minimal in ICU patients. Our results are in line with several controlled studies in non-ICU patients reporting that CM is of minimal negative impact (24–29). This finding may be seen as contradicting studies reporting increased mortality in patients developing CA-AKI (10, 11). Indeed, it is well established that CM contributes to the nephrotoxic burden experienced by ICU patients (30) and therefore cannot be considered harmless as this burden is associated with increased AKI incidence (Supplemental Fig. E3 and Table E5, Supplemental Digital Content 1, http://links.lww.com/CCM/A569). Actually, our results, rather than suggesting a total lack of CM toxicity, reveal that the specific added toxicity of CM seems minimal in ICU patients already suffering from multiple renal aggressions, in particular drug nephrotoxicity.

Risk Factors of CA-AKI

Our study shows that the SOFA score at the time of CM infusion is an ICU-specific risk factor alongside the concomitant use of other nephrotoxic agents. Conversely, risk factors identified outside of the ICU, e.g., diabetes mellitus, arterial hypertension, heart failure, chronic kidney failure, and cirrhosis (31), were not independently associated with CA-AKI (Table 3; and Supplemental Table E4, Supplemental Digital Content 1, http://links.lww.com/CCM/A569). Those findings are in

line with the results of the two other studies addressing ICU risk factors of CA-AKI. The nonrenal SOFA score in oncology critically ill patients (12) and vasoactive therapy, mean arterial pressure (both comprised in the SOFA score), serum creatinine at inclusion (renal component of the SOFA score), and diuretic treatment (nephrotoxic drug) in a less selective ICU population (11) were identified as independent risk factors for CA-AKI. Indeed, severity of disease and the high rate of concomitant nephrotoxic agents in ICU patients (as observed in this study) may outweigh the classical CA-AKI risk factors observed outside of the ICU, but this hypothesis should be confirmed in larger multicenter studies. Calculating the SOFA score and collecting the nephrotoxic agents are not cumbersome and were associated with good model performance in our population. This model would deserve external validation in a larger cohort.

Implications

First, our results do not support withholding CM infusion if it is deemed to enhance the diagnostic yield of an imaging procedure. Furthermore, the minimal toxic effect of CM may explain the negative studies addressing strategies aimed at preventing CA-AKI (32). Indeed, based on the present results, randomized trials in the ICU setting would need to include over 1,500 patients per group to be adequately powered, as the preventive intervention is unlikely to reduce AKI incidence below the value we observed in patients not receiving CM (at best, the absolute risk reduction we observed was 4.1% [95% CI, –4.6; 12.1%] in matched comparison).

Second, our findings reinforce the need for using in the critically ill, the term *contrast-associated AKI* rather than *contrast-induced AKI* as the toxicity of modern CM in the ICU is at best minimal and at worst diluted among other numerous factors of renal aggression.

Third, as reported (10), CA-AKI incidence markedly depends on the chosen definition (Fig. 2). This stresses the need for using, as done for AKI of other causes, a consensual definition for CA-AKI, such as the AKIN criteria (20).

Limitations of the Study

First, the use of potentially nephroprotective agents (32) was scarce (only 6% of contrast inclusions involved N-acetylcysteine or sodium bicarbonate administration), as opposed to the use of nephrotoxic agents (66% of all inclusions involved ≥1 nephrotoxic agent other than CM; Supplemental Table E1, Supplemental Digital Content 1, http://links.lww.com/CCM/A569). Similarly, the use of intraarterial CM was infrequent ($n = 27$ inclusions), and this route may be associated with high volumes of CM. This prevents drawing any conclusion about preventive measures, about other settings with less frequent use of nephrotoxic agents, and about the intraarterial route of CM administration.

Second, contrary to most other studies in the field, we included patients several times during their ICU stay (477 inclusions analyzed in 380 patients), and the multiple inclusions (in 20% of the patients) led to more complicated analysis of survival data (performed on patients included only once, thus preventing generalizability to patients with multiple inclusions). In fact, we believe that multiple inclusions are a strength of the study as clinical reality is better captured. Analyzing only the first inclusion in the course of ICU stay, as done in other studies, may be biased by subsequent CM infusions.

Third, our study was sufficiently powered to rule out a marked difference in AKI incidence between control and contrast inclusions on the basis of the observed absolute difference in AKI incidence and the fact that its 95% CI was narrow (Fig. 3). For mortality analysis, given the potential diagnostic benefit of CM and large 95% CI around the observed absolute difference in mortality, further studies are necessary. Similarly, other long-term outcomes (e.g., renal function at discharge) deserve evaluation.

Last, the choice of control inclusions may have an impact on our results. However, finding optimal control subjects in epidemiological studies is difficult. We aimed at including patients undergoing an intrahospital transfer without CM infusion rather than only including patients undergoing a CT scan without CM infusion, as physicians may be reluctant to infuse CM in patients they believe at higher risk of CA-AKI. Unfortunately, we only partially succeeded, as the majority of control inclusions were imaging procedures without CM infusion (Table 2). Nevertheless, our results are similar to those of Ng et al (12) (in oncology critically ill patients) using very different inclusion criteria for their control patients. A randomized study comparing CM and placebo infusion could overcome those difficulties, but would be very difficult, if not impossible to set up due to ethical reasons. Propensity-matched observational cohort studies, as performed in the present case, remain the only reasonable way to evaluate this issue.

CONCLUSIONS

CA-AKI occurred in 7% to 10% (AKIN definition) of ICU patients undergoing CM infusion, an incidence not significantly superior to that of AKI in matched control patients. Therefore, if a critically ill patient is transferred to an imaging facility, there is little reason to refrain from administering CM if it is deemed to enhance the diagnostic yield of the procedure. The toxic effect of modern CM appeared minimal but as it contributes to the overall nephrotoxic burden, preventive measures may still be considered at the time of CM infusion, at least in high-risk patients (i.e., with a high SOFA score and receiving other nephrotoxic agents). Further studies may evaluate the global nephrotoxic burden experienced by critically ill patients rather than focusing on the isolated specific impact of CM, which seems minimal.

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