

# A Retrospective Review of Contrast Nephropathy in a General Population

Asma Arayan, MD; Mark A. Nigogosyan, MD; Marvin J. Van Every, MD

## ABSTRACT

**Background:** One of the adverse events associated with administration of intravenous (IV) contrast media is contrast-induced nephropathy, yet its incidence is poorly characterized. We investigated the incidence of contrast-induced nephropathy in patients with elevated baseline serum creatinine concentrations who underwent computed tomography (CT) using IV contrast media.

**Materials and Methods:** Using the electronic medical records at a community hospital, we retrospectively identified patients with elevated baseline serum creatinine concentrations who had undergone CT utilizing IV contrast media between January and July 2000, a period prior to the routine use of pretreatment as prophylaxis against contrast-induced nephropathy, and who subsequently developed elevated serum creatinine. We identified concomitant risk factors for the rise in serum creatinine in these patients aside from IV contrast media exposure.

**Results:** One hundred ninety-three patients with a baseline serum creatinine concentration greater than 1.2 mg/dL underwent 236 CT studies utilizing IV low-osmolar contrast media. Nine of the 193 patients had a rise in serum creatinine  $\geq 0.5$  mg/dL up to 1 month later. None of these 9 patients had contrast exposure as the only risk factor for their rise in serum creatinine.

**Conclusion:** The role of IV contrast media in causing contrast-induced nephropathy and, thus, acute kidney injury, may be overestimated. Further study needs to be done into whether contrast-induced nephropathy is truly a common or even a real entity in patients receiving IV contrast media for routine studies who have no other risk factors for kidney injury warranting the expense, risks, and inconvenience of pretreatment.

poorly characterized. The reported incidence of contrast-induced nephropathy ranges from as low as 1%<sup>1</sup> to as high as 33%.<sup>2</sup> Many of these studies were done in cardiac patients receiving intra-arterial contrast. Other researchers have shown changes in serum creatinine to be similar in patients undergoing computed tomography (CT) with and without contrast.<sup>3</sup> These researchers also found that although reduced estimated glomerular filtration rate (GFR) is associated with higher risk of acute kidney injury as defined by serum creatinine, this risk is independent of exposure to contrast material.<sup>4</sup> Many risk factors have been suggested, including advanced age, diabetes mellitus, and multiple myeloma. Therefore, we conducted a retrospective review to determine the incidence of contrast-induced nephropathy in patients with elevated baseline serum creatinine concentrations after undergoing CT scans using IV contrast media.

## INTRODUCTION

Despite being one of the chief adverse events associated with administration of intravenous (IV) contrast media, contrast-induced nephropathy and its incidence and pathophysiology are

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**Author Affiliations:** Department of Medical Education, Gunderson Medical Foundation, La Crosse, Wis (Arayan); Department of Radiology (Nigogosyan); Department of Urology (Van Every), Gunderson Health System, La Crosse, Wis.

**Corresponding Author:** Marvin J. Van Every, MD, Mail Stop C04-004, Gunderson Health System, 1900 South Ave, La Crosse, WI 54601; phone 608.775.2212; fax 608.775.6756; e-mail mjvaneve@gundersenhealth.org.

## METHODS

Following approval of our application for a Health Insurance Portability and Accountability Act (HIPAA) waiver, we queried the electronic medical record database at a community hospital to retrospectively identify all patients with baseline serum creatinine concentrations between 1.2 mg/dL and 2.5 mg/dL who underwent CT utilizing IV contrast media between January and July 2000 and had a repeat serum creatinine drawn within 1 month of having the CT. These dates were chosen because this was before we used IV hydration or acetylcysteine as a prophylactic measure in patients receiving IV contrast. During the study period, no form of pretreatment was used routinely for renal protection. We used the lower limit of 1.2 mg/dL for serum creatinine because few people with serum creatinine above 1.2 mg/dL have normal renal function. We used the upper limit of 2.5 mg/dL because

**Table.** Details of 9 Patients Who Developed Nephropathy After Contrast-Enhanced Computed Tomography (CT) Scan

Age/Sex	IV Contrast	Pre-CT Day of Baseline SCr	Baseline SCr mg/dL	Post-CT Day	Post-CT SCr, mg/dL	Time From CT to Death	Comorbidities/Course
62/Male	Iohexol 140 ml	31	1.4	31 -60	1.9 1.3	<4 mo	DM2, pancreatic cancer, large cell lymphoma, CAD, CHF, HTN, DJD. Upset stomach and weight loss with endoscopy-proven GERD unresponsive to PPI. CT A+P showed progressive liver met and new primary pancreatic lesion. Gemcitabine at 2 wks and 3 wks after CT.
71/Female	Iopamidol 100 ml	0	1.6	10	4.2	<5 mo	Metastatic renal cell cancer (lungs), right ureteral stricture with stenosis, s/p L nephrectomy, breast cancer, carcinoid syndrome. New hepatic mets and a likely right peri-ureteral met; monitoring CT done. Admitted for scheduled stent change; returned 3 days later with ureteral obstruction; stent replaced. Obstructed again; percutaneous nephrostomy 2 days later.
64/Male	Iohexol 140 ml	2	1.4	8 21	1.9 1.4	>6 y	MGUS, HTN, CKD, hernias. CT A+P after several months of abdominal pain (no findings). Concurrent lab results notable for MGUS. Bilateral renal artery stenosis 6 years later.
59/Female	Iohexol 100 ml	0	1.5	13 14 15 17	2.0 1.7 1.4 1.2	1 y	Metastatic breast cancer, HTN. CT confirmed liver mets. Admitted 1 wk later for new back pain from pathologic fracture with dehydration and hypercalcemia, which improved with treatment.
60/Male	Iopamidol 100 ml	9	1.3	3 26 55 84	1.5 2.2 1.9 1.4	>12 y	CHF, pericarditis, GERD, pulm HTN, CAD, Linguinal hernia, small cell lung cancer, COPD, OSA. Bronchogenic small-cell lung cancer; first CT done for planning. Treated with cisplatin daily for 3 days with etoposide, then radiation planning with second CT (1 mo after first CT). Cisplatin/etoposide daily for 3 days, 3 wks later, and again after 3 more wks. Trouble swallowing related to chemotherapy. CT scans each with 100 ml iopamidol (SCr values are for days after second CT).
64/Male	Iohexol 140 ml	0	1.4	1 2 3 7	1.5 1.8 2.9 3.7	1 wk	Crohn's disease, Barrett esophagus. Elective lap Nissen and hiatal hernia repair. Admitted 5 days later with perforated stomach, surgically repaired. Discharged after 10 days, but readmitted next day with repeat perforation; repaired surgically. Septic shock and progressive multi-system organ failure with candida and <i>Pseudomonas peritonitis</i> with a fistula between the stomach and the chest. CVVH started. On amphotericin, piperacillin/ tazobactam and on pressors continually. Autopsy found chemical pneumonitis.
62/Female	Iohexol 140 ml	7	1.7	19 41 45 47 54 73	2.2 3.0 3.4 2.5 2.1 1.7	5 mo	DM2, metastatic breast cancer to retroperitoneal nodes, ascites, ureteral obstruction with ureteral stents in place, DVT. Radical mastectomy, chemotherapy in the past, adjuvant tamoxifen with recurrent disease treated with more repeated chemotherapy seen with increased ascites and decreased PO intake. Furosemide increased in addition to continued spironolactone and megestrol restarted. CT A+P 1 wk later to evaluate ascites- stents seem to be working appropriately. Admitted for ascites with paracentesis on post-CT day 45; discharged day 47.
92/Male	Iohexol 140 ml 140 ml	0	1.7	1 8 14	1.9 2.8 2.1	>6 mo	Alzheimer dementia, lung mass, cecal cancer, ascites, liver mass, lymph nodes. Admitted with hip pain after fall; discharged, then re-admitted 2 days later with confusion; KUB showed dilated loops of small bowel. CT A+P 3 days later, discharged next day. 1 wk later hospitalized for 6 days for agitation and rash; decreased PO (by mouth) intake thought to be cause of elevated creatinine.

**Table (continued).** Details of 9 Patients Who Developed Nephropathy After Contrast-Enhanced Computed Tomography (CT) Scan

Age/Sex	IV Contrast	Pre-CT	Baseline	Post-CT Day	Post-CT SCr, mg/dL	Time From CT to Death	Comorbidities/Course
		Day of Baseline SCr	SCr mg/dL				
63/Male	Iohexol 140 ml	0	1.3	2	1.3	>9 mo	Anaplastic large cell lymphoma, RUE DVT, zoster; ACE use. Admitted and discharged 2 wks later with cellulitis and RUE DVT that progressed to SVC thrombosis with resultant PE. Chemotherapy for anaplastic large cell lymphoma (CHOP then ICE- ifosfamide, carboplatin, etoposide). CT chest with contrast done twice: 6 days and 8 days after admission. ACE- cytarabine, etoposide, cisplatin admission. ACE- cytarabine, etoposide, cisplatin chemotherapy 4 days after first CT. (SCr values are for days after first CT)
				3	1.9		
				4	1.4		
				5	1.5		
				6	1.7		
				7	1.9		
				8	2.0		
				22	1.7		
29	1.3						

Abbreviations = DM2, diabetes mellitus type 2; CAD, coronary artery disease; PPI, proton-pump inhibitor; met, metastases; CHF, congestive heart failure; OSA, obstructive sleep apnea syndrome; HTN, hypertension; DJD, degenerative joint disease; GERD, gastroesophageal reflux disease; CT A+P, computed tomography of the abdomen and pelvis; MGUS, monoclonal gammopathy of undetermined significance; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; DVT, deep vein thrombosis; SVC, superior vena cava; PE, pulmonary embolism; CVVH, continuous veno-venous hemofiltration; ACE, angiotensin-converting enzyme; KUB, kidney, ureter, and bladder x-ray; RUE, right upper extremity; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone therapy

patients with serum creatinine higher than this were less likely to have contrast CT scans. Only 3 of our 193 patients had serum creatinine >2.0 mg/dL, and another 2 had a serum creatinine of 2.0 mg/dL. All patients received low-osmolar contrast material, either 100 ml iopamidol or 88 to 140 ml iohexol. The dose varied depending upon the regions of the body being evaluated. Evidence suggests that the incidence of contrast-induced nephropathy may be influenced by route of administration,<sup>5</sup> so we excluded patients who received intra-arterial contrast media.

The primary outcome measure was a post-CT serum creatinine rise of  $\geq 0.5$  mg/dL from baseline. We chose this degree of change because it is unequivocally categorized as acute kidney injury by the Acute Kidney Injury Network, which defines acute kidney injury as an increase of 0.3 mg/dL or more.<sup>6</sup> We also chose it because smaller fluctuations could be attributed to laboratory error or hydration status. Additionally, contrast-induced nephropathy has been defined as an increase of 25% in baseline serum creatinine, and this represents an increase of 25% or more in our patient population, except for the 3 patients whose serum creatinine was >2.0 mg/dL.

After the patients were identified, their medical records were retrospectively reviewed to determine whether they had any risk factors for acute kidney injury aside from IV contrast media exposure.<sup>6</sup> Based on the other risk factors identified in each patient, we determined whether IV contrast media administration was likely to have been the main cause of the rise in serum creatinine.

## RESULTS

One hundred ninety-three patients with a baseline serum creatinine concentration greater than 1.2 mg/dL underwent 236 CT studies utilizing IV low-osmolar contrast media. Nine of the 193 (4.7%) patients had a rise in serum creatinine  $\geq 0.5$  mg/dL up to 1 month later and all of their baseline serum creatinine levels were 1.3 to 1.7.

None of these 9 patients had contrast exposure as the only risk factor for their rise in serum creatinine.

Nineteen of the 193 patients had baseline serum creatinine greater than or equal to 1.8, but none of these patients developed a greater than or equal to 0.5mg/dL rise in creatinine. Forty-two of the 193 patients had diabetes mellitus type 2, and 2 of 193 had diabetes mellitus type 1. Neither of the 2 patients with type 1 diabetes developed a rise in serum creatinine, and 2 of the 42 patients with type 2 diabetes (4.8%) developed a rise in serum creatinine greater than or equal to 0.5mg/dL.

Of the 9 patients with rise in serum creatinine, our youngest patient was aged 59 years, and our oldest patient was aged 92 years. Three of our 9 patients were women. One of 9 patients underwent 2 CT studies 2 days apart, and another had 2 CT studies about a month apart. The remaining 7 patients had only 1 CT study during the study period. Details of patient comorbidities, course of treatment, and serum creatinine values after CT scan with contrast are provided in the Table.

Eight of the 9 patients had an oncologic diagnosis. Of these, 3 received nephrotoxic chemotherapy and a fourth received non-nephrotoxic but dehydration-producing chemotherapy combined with increased furosemide. The only patient who did not have a malignant diagnosis had Crohn's disease and developed renal injury after contrast exposure when he was hospitalized for a perforated bowel. He went on to develop multisystem organ failure due to sepsis and died 1 week after his contrast study, at which time the renal injury was noted. Two of 9 patients had type 2 diabetes mellitus, and 4 of 9 had hypertension, both of which are risk factors for kidney disease. One of the 9 patients had a solitary kidney and had repeated obstruction of that kidney. Seven of our 9 patients died of nontraumatic causes within 2 years after developing nephropathy.

## DISCUSSION

The results of this retrospective review show that contrast-induced nephropathy in patients with elevated baseline serum creatinine is an uncommon occurrence. All of the 9 patients who developed what would clinically be considered contrast-induced nephropathy had risk factors in addition to IV contrast media exposure for the measured increase in serum creatinine concentration. Additionally, the incidence of nephropathy after undergoing CT with contrast in our cohort was only 3.8% of 236 contrast CT studies performed (4.7% of 193 individual patients), which is lower than the published incidence in patients with higher risk.<sup>7</sup>

Even though contrast-induced nephropathy has been a named entity for years, the pathophysiology is not well understood. Contrast-induced nephropathy is thought to have multiple possible mechanisms, among them “alterations in renal hemodynamics, rheological properties, endocrine and paracrine factors (adenosine, endothelin, and reactive oxygen species), hyperosmolar and hyperviscous alterations of intratubular fluids,” and “direct cytotoxic effects on renal tubular cells.”<sup>8</sup> Iso-osmolar and low-osmolar contrast media are less likely than other types of contrast to be associated with contrast-induced nephropathy. Multiple studies have been conducted to determine what interventions minimize the nephrotoxicity of contrast media, but only periprocedural IV hydration has been suggested as a preventive measure. It is thought that patients with certain risk factors, including worse baseline renal function, diabetes mellitus, and advanced age, are more prone to contrast-induced nephropathy than those without risk factors. Therefore, when patients with risk factors undergo contrast media exposure, much care is taken to prevent contrast-induced nephropathy by using periprocedural hydration. It is interesting to note that our patients with diabetes developed a rise in serum creatinine greater than or equal to 0.5mg/dL at a rate similar to that of our entire study population: 4.8% and 4.7%, respectively.

There are few randomized controlled trials differentiating the incidence of contrast-induced nephropathy in cohorts receiving IV contrast media from those receiving intra-arterial injections of contrast media. This is important because not only is the route of administration different, but also the amounts of contrast used are usually higher in intra-arterial exposures for coronary angiography and the patients are often more acutely ill. Additionally, arterial manipulation exposes patients to other forms of nephropathy, such as cholesterol embolization-induced acute kidney injury. This patient population may already be predisposed to acute renal failure/insufficiency because of their underlying vascular pathology and other medical comorbidities. Furthermore, few of these studies employed control groups to compare changes in serum creatinine for similarly ill patients who did not undergo iodinated contrast media exposure.

Similarly, there is question of whether contrast-induced nephropathy due to IV contrast media injection is a true clinical entity. Stratta et al<sup>8</sup> reviewed over 1000 papers on contrast-induced nephropathy and found little concordance regarding results. Newhouse et al<sup>7</sup> examined serum creatinine changes in the absence of iodinated contrast media exposure and found a higher percentage of patients with a significant elevation of their serum creatinine than we found in our patient population.<sup>7</sup> The rate of increase in serum creatinine by at least 0.6 mg/dL in the study for patients with a baseline of 0.6 to 1.2 mg/dL was 7% compared with 26% in patients with baseline of 2 mg/dL or higher. Therefore, one would expect our patient population (baseline 1.2-2.5 mg/dL) to have had at least a 7% to 26% prevalence of increase in serum creatinine even without contrast media injection. In fact, our prevalence should have been even higher because our cut off of 0.5 mg/dL change in serum creatinine is less than 0.6 mg/dL. In this same study,<sup>7</sup> the researchers also found that serum creatinine changes of magnitudes specified in both absolute serum creatinine in mg/dL and in percentage from baseline occurred as often and were of the same magnitude as published reports of contrast-induced nephropathy. None of these patients had received contrast media in the preceding 10 days, which is the usual time frame in which contrast-induced nephropathy occurs and improves. Thomsen and Morcos<sup>9,10</sup> also showed that absolute changes, as opposed to relative changes, in serum creatinine led to significant difference in contrast-induced nephropathy incidence in patients with elevated baseline serum creatinine.

Finally, the reported incidence of contrast-induced nephropathy ranges widely—as low as 1%<sup>1</sup> and as high as 33%,<sup>2</sup> suggesting that either contrast-induced nephropathy is not well defined, with multiple pathologic diseases being called contrast-induced nephropathy, or that IV contrast-induced nephropathy is not a true clinical entity.<sup>8</sup> Contrast-induced nephropathy itself is a clinically nebulous entity, and past published rates of contrast-induced nephropathy need to be evaluated within the context of the study populations, route of contrast administration, baseline renal function, and the amount of change from this baseline in the individual studies. Therefore, it is difficult to generalize the results from these studies. In particular, the *post hoc, ergo propter hoc* (after this, therefore because of this) argument is deceiving: just because measured renal function changes after iodinated contrast media exposure does not necessarily mean the change can be attributed to the exposure. This is true particularly because there are no large randomized control trials measuring renal dysfunction due to IV contrast media use after CT studies. The lack of control groups with patients who are similarly ill in these past studies makes it difficult to attribute kidney injury after IV iodinated contrast use to the contrast media alone.

In a pooled analysis of 2 randomized control trials of patients with glomerular filtration rates (GFR) <60 ml/min undergoing IV contrast media administration with CT imaging, Thomsen and Morcos<sup>10</sup> found that no patients in these studies needed any intervention other than observation after contrast-induced nephropathy was diagnosed. All the patients recovered back to their baseline. Furthermore, just as the reported incidence of contrast-induced nephropathy ranges widely, so does the rate requiring treatment other than observation. Some reports suggest that dialysis is required in 0.4% to >5% of patients.<sup>8</sup>

An interesting point raised by Stratta et al<sup>8</sup> is that contrast-induced nephropathy itself might be a marker for worsening renal and systemic prognosis. Patients prone to contrast-induced nephropathy usually have multiple medical comorbidities, and these comorbidities often are associated with increased risk for acute kidney injury and chronic kidney disease in general. This might be why patients who undergo coronary angiography develop contrast-induced nephropathy more commonly than we have found—the patients are more ill to begin with prior to their intra-arterial contrast media exposures. This suggests that otherwise healthy people with minimal risk factors for renal dysfunction also should be at minimal risk for contrast-induced nephropathy. With our study results, we suggest that this holds true even for people with elevated serum creatinine (1.2-2.5 mg/dL), and that patients who do go on to develop the clinical entity of contrast-induced nephropathy are those who already have a poor prognosis.<sup>10</sup> In fact, 7 of our 9 patients who developed contrast-induced nephropathy died within the following 2 years of nontraumatic causes.

Our study has a number of limitations. Our sample size is small, and the study is subject to the inherent weaknesses of a retrospective study. Furthermore, although we disparage the faulty logic used to support the contention that contrast-induced nephropathy is a true entity, we use the same logic to argue that patients with multiple risk factors for renal dysfunction who develop acute kidney injury do so because of these risk factors, not the IV contrast media. We also did not control for hospitalized or nonhospitalized CT studies performed, which may be important because patients who are hospitalized not only are more ill, but they also are more likely to be volume depleted and to have a host of other complicating conditions, such as fluctuations in blood pressure and exposure to nephrotoxic medications. Therefore, if most of the patients in our study were outpatients, the prevalence of contrast-induced nephropathy found likely would be lower than expected because these patients are less ill. Nonetheless, we believe that this is also a strength of our study because we are suggesting that patients undergoing routine outpatient CT scans utilizing IV contrast media have minimal risk of contrast-induced nephropathy.

## CONCLUSION

The role of IV contrast media in causing contrast-induced nephropathy and, thus, acute kidney injury, may be overestimated. Further studies with control groups are needed to determine whether contrast-induced nephropathy due to IV contrast media is first, a true entity and second, whether patients with chronic kidney disease are more at risk of developing contrast-induced nephropathy than people with normal renal function.

Currently, unwarranted concern about contrast-induced nephropathy often prevents us from obtaining contrast studies, thereby limiting our ability to accurately diagnose and treat our patients. Patients with decreased renal function at baseline are treated as being at higher risk for contrast-induced nephropathy, and periprocedural IV hydration often is used for patients prior to contrast media exposure. However, does IV contrast media for routine outpatient studies truly cause nephropathy? And does the risk of nephropathy warrant the expense, inconvenience, and possible complications of periprocedural IV hydration? We believe the importance of these questions warrants further investigation.

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