CT Angiography for Intracerebral Hemorrhage Does Not Increase Risk of Acute Nephropathy

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Background and Purpose—CT angiography (CTA) is receiving increased attention in intracerebral hemorrhage (ICH) for its role in ruling out vascular abnormalities and potentially predicting ongoing bleeding. Its use is limited by the concern for contrast induced nephropathy (CIN); however, the magnitude of this risk is not known.

Methods—We performed a retrospective analysis of a prospectively collected cohort of consecutive patients with ICH presenting to a single tertiary care hospital from 2002 to 2007. Demographic, clinical, and radiographic data were prospectively collected for all patients. Laboratory data and clinical course over the first 48 hours were retrospectively reviewed. Acute nephropathy was defined as any rise in creatinine of >25% or >0.5 mg/dL, such that the highest creatinine value was above 1.5 mg/dL.

Results—539 patients presented during the study period and had at least 2 creatinine measurements. 348 (65%) received a CTA. Acute nephropathy developed in 6% of patients who received a CTA and in 10% of those who did not ($P=0.1$). Risk of nephropathy was 14% in those receiving no contrast (130 patients), 5% in those receiving 1 contrast study (124 patients), and 6% in those receiving >1 contrast study (244 patients). Neither CTA nor any use of contrast predicted nephropathy in univariate or multivariate analysis.

Conclusion—The risk of acute nephropathy after ICH was not increased by use of CTA. Studies of CIN that do not include a control group may overestimate the influence of contrast. Patients with ICH appear to have an 8% risk of developing "Hospital-Acquired Nephropathy." **(*Stroke*. 2009;40:2393-2397.)**

Key Words: cerebral hemorrhage ■ tomography ■ X-ray computed ■ contrast media

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Vascular imaging is often performed in patients with intracerebral hemorrhage (ICH) to rule out vascular abnormalities. The most widely and rapidly available modality is CT angiography (CTA)[1]; 99% of U.S. emergency departments have 24-hour CT capability, and 95% use a multislice CT scanner.[2,3] The yield of CT angiographic examinations can be quite high in ICH.[4–7] In addition, there is growing interest in the use of CTA to predict hematoma expansion and clinical outcome.[8–10]

One limitation to the routine use of CTA is that contrast dye is thought to be nephrotoxic, carrying the risk of contrast induced nephropathy (CIN).[11] However, the risk of CIN after ICH is unclear. First, many studies of CIN have examined the use of intraarterial contrast during intracardiac procedures, and it is unclear whether these risk estimates also apply to intravenous administration or to patients not undergoing cardiac catheterization.[12,13] Second, CIN is defined as a creatinine rise after the use of a contrast agent, and many studies have not included a control group to examine creatinine rise in the absence of contrast.[14] In fact, when a control group is included, it becomes quite difficult to uncover an increased rate of nephropathy.[14] As a result, the risk of CIN may be substantially overstated in the literature.[15]

In patients with cerebrovascular emergencies, the risk of CIN is thought to be low. Retrospective studies have found CIN occurring in 2% to 3% of patients, with none requiring dialysis or suffering permanent kidney dysfunction.[16–18] However, ICH is a disease with high morbidity and mortality,[19,20] much of it likely attributable to in-hospital complications,[21,22] and these patients may be at risk of acute nephropathy independent of contrast administration.

To estimate the risk of renal injury after ICH, and the extent to which CTA use increases this risk, we retrospectively reviewed a cohort of consecutive patients with ICH for contrast agent use and serial creatinine measurements.

Methods

Patient Selection and Data Collection

This was a retrospective review of a prospectively collected cohort of consecutive patients with acute ICH who presented to Massachusetts

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General Hospital from January 1, 2002 to December 31, 2007.[8,20,23] Patients with secondary causes of ICH were excluded. In addition, patients were excluded for lack of an admission creatinine value and for lack of at least 1 further creatinine measurement within 48 hours of the baseline test. All aspects of the study were approved by the Institutional Review Board.

Clinical data was captured prospectively as previously described,[8,20,23] including history of diabetes (DM), hypertension (HTN), coronary artery disease (CAD), admission systolic blood pressure (SBP), and diastolic blood pressure (DBP). Admission Glasgow Coma Scale (GCS) score was recorded from the emergency department (ED) note or admission note when available. Long-term outcome was captured as previously described.[8,22,24]

To determine serial creatinine values, clinical course, and incidence of clinically relevant renal injury, a structured medical record review was performed. For patients with any abnormal creatinine level, admission notes, consultation notes, discharge summaries, radiology reports, autopsy reports, creatinine levels, and paper charts were reviewed. Diagnoses that were preexisting or present on arrival including acute renal failure (ARF), chronic renal insufficiency (CRI), and end-stage renal disease (ESRD) were captured. Radiology reports were reviewed for all studies using any form of contrast.

To estimate glomerular filtration rate (GFR) we used the MDRD equation,[25,26] and all GFR measures were analyzed as mL/min/1.73m^2. Acute nephropathy was defined as any rise in creatinine of >25% or >0.5 mg/dL,[27] such that the highest creatinine was above 1.5 mg/dL (the upper limit of normal in our hospital) within 48 hours. Clinically relevant renal injury was operationally defined as any change in clinical course, prolonged clinical course, or need for dialysis.

CT angiography was performed with a standardized protocol at the discretion of the clinical care team.[28] Hematoma location was categorized on the basis of the CT scan by one of the study neurologists based on previously established criteria.[20] The presence of intraventricular hemorrhage (IVH) was scored as a dichotomous variable.

Data Analysis

Continuous variables with normal distributions were analyzed with Student *t* test, and those with nonnormal distributions were analyzed with the Kruskal-Wallis test. Dichotomous variables were analyzed with Fisher exact test. Multivariable analysis for development of nephropathy was performed with a backward selection logistic regression model, including variables associated ($P<0.2$) in univariate analysis (age, DM, SBP, white race, glucose, GCS, GFR), and removing variables in a stepwise fashion for $P>0.1$. CTA use was forced into the model. Multivariable analysis of 90-day mortality was analyzed with a Cox proportional hazards model. All analyses were performed with Stata software (Stata Corp).

Results

A total of 682 patients with ICH presented during the study period. 142 patients were excluded for lack of either a baseline or a followup creatinine value, leaving 539 patients for analysis. Of these patients, 348 (65%) underwent CTA, and 41 (8%) developed acute nephropathy. A univariate analysis of demographic factors associated with CTA performance is shown in Table 1. There was no significant difference in rate of nephropathy (using the definition commonly applied for CIN[27]) among those receiving a CTA. There was also no difference in development of renal injury requiring a change in management (2.6% versus 1.4%, $P=0.3$)

We next examined clinical features, including CTA use, that might predict development of acute nephropathy. Table 2 shows that patients with this complication were disproportionately male, diabetic, and had a history of hypertension. It did not appear that CTA use increased the risk of nephropathy.

Table 1. Univariate Analysis of Demographic Factors Associated With CTA Performance

	No CTA Performed n=191 (35%)	CTA Performed n=348 (65%)	*P* Value
Age	75 (66–83)	72 (62–80)	0.01
Female sex	40%	45%	0.3
White race	84%	86%	0.5
Past medical history			
CAD	22%	18%	0.2
DM	26%	18%	0.05
HTN	91%	76%	<0.001
Any renal diagnosis	13%	4.6%	0.04
ARF	13%	11%	
CRI	45%	39%	
ESRD	16%	22%	
Other	25%	19%	
Clinical features			
Initial SBP	186 (160–210)	178 (152–200)	0.02
Initial DBP	93 (78–106)	90 (78–106)	0.5
Serum glucose	139 (112–180)	136 (111–170)	0.2
GCS score	14 (7–15)	14 (8–15)	0.9
ICH location			
Lobar	23%	40%	
Deep	57%	41%	
Mixed	9%	4%	
Cerebellar	6%	13%	
Primary IVH	1%	0%	
Brainstem	4%	2%	0.01
Any IVH present	45%	56%	0.02
Initial creatinine	1.1 (0.9–1.5)	1.0 (0.8–1.2)	0.0003
Initial creatinine >1.5	22%	6%	<0.0001
Initial GFR	64 (45–84)	73 (57–87)	0.0002
Initial GFR <60	43%	29%	0.001
Development of nephropathy	10%	6%	0.1
Development of clinically relevant renal injury	2.6%	1.4%	0.3

Continuous variables are presented as median (interquartile range).

It is possible that some patients received contrast other than through CTA. To evaluate this, we determined the total number of contrast-related radiographic studies performed over the first 48 hours. Nephropathy occurred in 14% of those receiving no contrast (130 patients), 5% of those receiving 1 such study (124 patients), 7% in those receiving 2 studies (209 patients), and 3% of those receiving more than 2 studies (35 patients). There was no relationship between number of studies and risk of nephropathy ($P=0.2$, Fisher exact).

Multivariable analysis was performed to determine whether CTA use is an independent predictor of acute nephropathy. Table 3 shows that after controlling for DM, GCS score, GFR, SBP, race, and sex, there was no significant

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Table 2. Univariate Analysis of Predictors of Acute Nephropathy

	No Nephropathy n=498 (92%)	Nephropathy n=41 (8%)	*P* Value
Age	74 (63–81)	68 (58–74)	0.007
Female sex	45%	22%	0.005
White race	87%	63%	<0.001
Past medical history			
CAD	18%	32%	0.06
DM	18%	51%	<0.001
HTN	80%	95%	0.02
Any renal diagnosis	4%	49%	<0.001
ARF	5%	16%	
CRI	41%	42%	
ESRD	10%	37%	
Other	45%	26%	
Clinical features			
SBP	180 (152–200)	214 (184–236)	0.0001
DBP	90 (78–105)	110 (90–122)	0.0001
Serum glucose	134 (110–169)	182 (155–226)	0.0001
GCS score	14 (8–15)	6 (3–8)	0.0001
ICH location			
Lobar	36%	10%	
Deep	45%	73%	
Mixed	6%	2%	
Cerebellar	10%	12%	
Primary IVH	0.4%	0%	
Brainstem	3%	2%	0.04
Any IVH	49%	82%	<0.0001
Initial creatinine	1.0 (0.8–1.2)	1.3 (1.1–2.5)	<0.0001
Initial creatinine >1.5	9%	44%	<0.0001
Initial GFR	71 (55–87)	57 (23–70)	0.0001
Initial GFR <60	33%	54%	0.01
CTA performed	65%	54%	0.1
Development of clinically relevant renal injury	0.6%	14%	<0.001

effect of CTA use. Although lower GFR was an independent predictor of acute nephropathy, this effect was nonlinear; the risk was 53% in those with GFR <20, 14% in those with GFR 20 to 40, 7% in those with GFR 40 to 80, and 3% in those with GFR >80. Similarly, the effect of SBP was nonlinear; the risk of acute nephropathy was 3% in those with SBP <180, 6% in those with SBP 180 to 220, 20% in those with SBP 220 to 240, and 31% in those with SBP >240.

Table 3. Multivariable Analysis of Risk Factors for Developing Nephropathy

Variable	OR (95% CI)	*P* Value
History of DM	4.3 (1.9–9.7)	<0.0001
GCS score (per unit better)	0.8 (0.7–0.9)	<0.0001
GFR (by 10 mL/min/1.73m^2 increase)	0.7 (0.6–0.8)	<0.0001
SBP (per 10-mm Hg increase)	1.2 (1.1–1.3)	0.002
White race	0.3 (0.1–0.6)	0.002
Female sex	0.3 (0.1–0.8)	0.01
CTA	1.4 (0.6–3.2)	0.4

To evaluate whether development of acute nephropathy is a risk factor for poor outcome, we performed a multivariable analysis of predictors of survival over the first 90 days after ICH. We found no effect of acute nephropathy on 90 day mortality (HR 1.2, 95% CI 0.7 to 1.8, $P=0.6$).

To determine the clinical relevance of acute nephropathy, we performed a structured medical record review of all patients with elevated creatinine values to determine the frequency with which patients developed clinically relevant renal injury requiring a change in management. Ten patients met this criterion, and Table 4 describes these clinical events. Of these patients, 50% received a CTA, and 70% received a contrast study of any kind. There were not enough events to perform a multivariable analysis examining the association of contrast exposure with outcome.

It is possible that baseline kidney function is an effect modifier of any relationship between CTA and acute nephropathy. We therefore performed 2 subgroup analyses, stratifying patients by GFR on presentation. After multivariable analysis of patients with an initially normal GFR (>60), independent predictors of nephropathy included diabetes (OR 6.0, 95%CI 1.9 to 19, $P=0.002$), presence of intraventricular blood (OR 8.7, 95%CI 1.0 to 75, $P=0.05$), and elevated SBP (OR 1.2, 95%CI 1.0 to 1.4, $P=0.04$). Neither CTA (OR 1.8, 95% CI 0.4 to 7.9, $P=0.4$) nor any contrast use (OR 0.9, 95% CI 0.3 to 3.3, $P=0.9$) independently predicted nephropathy in this subgroup. In patients with a low GFR on presentation (<60), the only independent predictor of nephropathy was diabetes (OR 3.5, 95%CI 1.2 to 10, $P=0.02$). There was no effect of CTA (OR 0.6, 95%CI 0.2 to 2.0, $P=0.4$) or any other contrast use (OR 0.8, 95%CI 0.2 to 3.0, $P=0.8$). Even among those subgroups with GFR <40 or GFR <30, there was no effect of CTA use on development of nephropathy (data not shown).

Discussion

Patients with ICH appear to have a risk of "Hospital-Acquired Nephropathy" of approximately 8%, with no evidence that use of a contrast agent increases this risk. These patients may be at risk of renal injury because many of the same risk factors for nephropathy are also risk factors for developing ICH.[29] ICH victims suffer a range of complications, including thrombotic, respiratory, and neurological[21,22,30]; it appears that renal complications are relatively common as well.

Our findings suggest that any contribution of CTA to the development of nephropathy after ICH is probably lower than previously estimated. Although the incidence of CIN has been suggested to be 2% to 3% in patients with cerebrovascular emergencies,[16–18] these studies only examined patients receiving contrast. The lack of control groups makes it difficult to estimate the independent contribution of contrast administration to this event. Some have suggested that the term "contrast-induced nephropathy" can be misleading, as no contrast is required for this event to occur.[15] Even among patients who develop nephropathy, most experience no clin-

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Table 4. Clinical Features of Patients Suffering Clinically Relevant Renal Injury

Patient	Age	Sex	Contrast	Clinical Course
1.	69	Male	None	Initial creatinine (2.5) rose after 48 hours because of obstructive uropathy. Patient was diagnosed with urethral stricture and treated with dilatation.
2.	66	Male	None	Developed heart failure, nephritic syndrome, worsening cardiogenic shock, hypotension, and was placed on dialysis.
3.	82	Male	None	A creatinine rise from 1.6 to 3 was ascribed to mannitol use. Patient was treated with lasix and hydration.
4.	72	Male	None Two contrast studies	Creatinine rose from 3.5 to 4.7. Patient had a history of polycystic kidney disease and was diagnosed with Acute Tubular Necrosis.
5.	86	Male	None Two contrast studies	Creatinine was stable at 1.9 over 48 hours but at day 20 rose to 3.0. Patient was diagnosed with intrinsic renal disease.
6.	58	Female	CTA One other contrast study	Creatinine rose from 1.6 to 2.6. Patient developed pulmonary edema, ascribed to acute renal dysfunction. Patient treated with furosemide, fluids, and bilevel positive airway pressure.
7.	53	Male	CTA	Creatinine rose from 0.5 to 3.1. This occurred in the setting of multiple doses of mannitol, acute myocardial infarction, pneumonia, EVD infection, and episodes of hypotension.
8.	78	Male	CTA One other contrast study	Creatinine rose from 1.6 to 2.1. Patient was diagnosed with prerenal azotemia and given IV fluids.
9.	68	Male	CTA One other contrast study	Creatinine rose from 1.2 to 3. This occurred in the setting of mannitol use, aspiration pneumonia, and institution of palliative care measures.
10.	79	Female	CTA	Creatinine rose from 1.0 to 2.4. This occurred in the setting of ventricular tachycardia, torsades de pointes, acute coronary syndrome, and multisystem organ failure.

ically meaningful impact or change in management. Therefore, the routine performance of CTA is probably safe (from a renal perspective) for the majority of patients with ICH.

The major limitation of this study is its retrospective nonrandomized design. Patients received CTA (or any other contrast agent) at the discretion of the clinical providers. As a result, it may be that clinical judgment withheld CTA from those at highest risk of nephropathy. We attempted to control for this with multivariable analysis and subgroup analyses examining only those patients at highest risk. Unfortunately, the possibility remains that factors went into this clinical judgment we could not control for. Another limitation is that we could not easily obtain exact dosing of contrast in each study, and we were forced to approximate contrast dose exposure by number of contrast studies. However, because we saw no trend toward an effect, it is not clear that adjusting for exact dose would change our results.

In conclusion, the risk of nephropathy after CTA in patients with ICH is not significantly different from the risk without CTA. Emergency CTA is gaining increasing use in ICH, as it can accurately diagnose vascular malformations and be used for surgical planning.[2,7] There is also increasing interest in the use of CTA for risk stratification of candidates for therapies aimed at preventing hematoma expansion. Evidence of contrast extravasation, or a "Spot Sign" on CTA, may predict subsequent hematoma expansion,[8–10] and emergency use of CTA may be practical in guiding therapy. Clinical trials and clinical pathways incorporating the routine use of emergency CTA to guide therapy will need to clearly balance the risks and benefits of this technology. Our results here suggest that those risks are likely extremely low. Patients with ICH are at risk of developing "Hospital-Acquired Nephropathy" but it does not appear that CTA use increases this risk.

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Dr Lev has received consulting fees from Vernalis, is on the medical advisory board for CoAxia, and has received speaking fees, research support, and is on the medical advisory board for GE Healthcare. Dr Goldstein has received consulting fees from CSL Behring and Genentech.

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