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Renal Safety of CT Angiography and Perfusion Imaging in the Emergency Evaluation of Acute Stroke

BACKGROUND AND PURPOSE: Multimodal CT imaging with contrast-enhanced CT angiography (CTA) and CT perfusion (CTP) is increasingly being used to guide emergency management of acute stroke. However, little has been reported about the safety of intravenous contrast administration associated with these studies in the acute stroke population, including cases in which baseline creatinine values are unknown. We investigated the incidence of contrast-induced nephropathy (CIN), defined as a 25% or more increase in baseline creatinine levels within 72 hours of contrast administration and chronic kidney disease in patients receiving CTA±CTP at our regional stroke center.

MATERIALS AND METHODS: We analyzed 198 patients who underwent contrast CT studies for evaluation of acute ischemic or hemorrhagic stroke at our center (2003–2007). Through retrospective chart abstraction, we analyzed serial creatinine levels (baseline to day 3) and later values (≥day 4) where available. The incidences of CIN and/or chronic kidney disease were documented. After power analysis, CIN and non-CIN groups were compared by using the unpaired t test, Wilcoxon rank sum test, or Fisher exact test.

RESULTS: None of the 198 patients developed chronic kidney disease or required dialysis. Of 175 patients with serial creatinine measurements between baseline and day 3, 5 (2.9%) developed CIN. The incidence of CIN was 2% in patients who were scanned before a baseline creatinine level was available.

CONCLUSION: The incidence of renal sequelae is relatively low in acute stroke patients undergoing emergent multimodal CT scanning. Prompt CTA/CTP imaging of acute stroke, if indicated, need not be delayed in those with no history of renal impairment.

Multimodal CT scanning is increasingly being used to aid acute stroke diagnosis and management. Dynamic CT perfusion (CTP) differentiates thresholds of reversible and irreversible ischemia and, thus, helps to identify "tissue at risk" that is potentially salvageable with thrombolytic therapy.[1-4] CT angiography (CTA) allows for rapid noninvasive assessment of the intracranial and extracranial vasculature and identifies vessel occlusions or stenoses that may be amenable to acute treatment.[1-4] For intracerebral hemorrhage, CTA can identify secondary causes of hemorrhage, and, in the acute phase, the CTA "spot sign" can predict which hemorrhages are likely to expand.[5-7] Advantages of multimodal CT over MR imaging include its rapid accessibility, lower costs, shorter scanning time intervals, better patient tolerability, and higher spatial resolution.[8,9] Although it is not yet clear whether the information provided by multimodal CT improves stroke outcomes, the increasing use of these imaging methods warrants more thorough assessment of their safety profiles.

Little has been reported regarding the safety of multimodal CT imaging in the acute setting. Because "time is brain" for acute stroke patients,[10] some stroke centers perform such imaging immediately on patient arrival to the emergency department, often before the results of blood work (eg, creatinine) are available. The primary safety concern regarding contrast-enhanced CT is the potential development of contrast-induced nephropathy (CIN), defined as a 25% or more increase in baseline creatinine levels within 72 hours of contrast administration.[11,12] Some clinicians feel uneasy about ordering contrast studies given the potential for CIN and the difficulty in obtaining a reliable history of renal disease in acute stroke patients who are frequently incapacitated or unable to communicate. In patients with CIN, creatinine levels usually peak around days 2–3 and normalize within 2 weeks, but a small proportion go on to chronic renal failure and dialysis.[11,13] CIN has been associated with prolonged hospital stay, increased resource use, and a fivefold increase in mortality.[12,14,15]

This purpose of this study was to assess the renal safety of emergency multimodal CT scanning in acute stroke patients at a large regional stroke center, including those patients for whom the baseline creatinine level was not known.

Materials and Methods

We identified all of the patients who presented to the emergency department of our stroke center with a suspected acute stroke between January 2003 and August 2007 and received a CTA and/or CTP study. For this study, we included acute ischemic stroke patients who underwent CTA and CTP within 3 hours of symptom onset, and acute

hemorrhagic stroke patients who received CTA within 24 hours of onset. Through retrospective chart abstraction, we determined the incidence of acute and chronic renal impairment as a result of non-ionic contrast administration. This study received approval by our local research ethics board.

In our region, a city-wide prehospital activation protocol is in effect, whereby ambulances transport patients with acute stroke symptoms directly to our center (bypassing the nearest hospitals) for initial consultation and treatment. After stabilization, these patients are repatriated back to local hospitals. We use an acute stroke CT imaging protocol composed of an immediate noncontrast head CT, CTA from arch to vertex, and CTP study after initial review by the consulting neurologist. Many acute intracerebral hemorrhage patients are now receiving CTA as part of the initial imaging protocol. All of the acute stroke patients arriving under the ambulance redirect protocol are assessed urgently by a 24/7 on-call stroke team that includes a staff neurologist. Published benchmarks are followed for acute stroke assessment, including a target "door-to-CT scan" time of under 25 minutes.[16] We routinely screen for a history of chronic kidney disease from the patient, the patient's family, or from the hospital chart. Blood work is drawn before initial scanning, but if there is no known history of chronic kidney disease, imaging is often performed before the creatinine results are available to prevent undue imaging and treatment delays. A baseline serum creatinine result is always reviewed before scanning in patients with a known or suspected history of chronic kidney disease. Contrast is not generally administered to these patients if the calculated glomerular filtration rate (GFR) by using the Cockcroft-Gault equation is 30 mL/min or less. Therefore, such patients are excluded from the present analysis. Patients with renal disease are scanned if the creatinine value is available, provided that the calculated GFR is 30 mL/min or more. Serial creatinine values are not available at our institution for the substantial proportion of patients who do not qualify for thrombolysis and are repatriated to their local hospitals after emergency assessment. It is not possible to assess the development of CIN in repatriated patients, and, therefore, they are excluded from this study.

The ischemic CT stroke protocol, performed on a 64-section CT scanner (VCT; GE Healthcare, Milwaukee, Wis), includes a precontrast and postcontrast CT head with parameters: 120 kVp, 340 mA, 8- × 5-mm collimation, 1 second per rotation, and table speed 15 mm per rotation. A CTA was performed from aortic arch to vertex with the following parameters: 0.7 mL/kg of iodinated contrast agent up to a maximum 90 mL (nonionic, low osmolar iohexol [Omnipaque], 300 mg of iodine/mL; GE Healthcare, Piscataway, NJ; or nonionic, iso-osmolar iodixanol [Visipaque], 300 mg of iodine/mL, GE Healthcare); 5- to 10-second delay, 120 kVp, 270 mA, 1 second per rotation, 1.25-mm-thick sections, and table speed 3.7 mm per rotation. After the CTA series, a CTP study was usually performed. Scan parameters for the CTP were as follows: 80 kVp, 190 mA, and 0.5 mL/kg (maximum 40 mL) iodinated contrast agent (Omnipaque or Visipaque) injected at 4 mL/s with a 3- to 5-second delay. The CT protocol for hemorrhagic stroke was similar but did not include CTP. Scan times for each part of the acute stroke protocol were as follows: CT head, 14 seconds; CTA, 30–40 seconds (including contrast delay); and CTP, 45 seconds. Scan set up time took up to 2 minutes. CT technologists performed all of the postprocessing, including multiplanar reformats at the CT operator's console. Coronal and sagittal multiplanar reformat images were created as 10-mm-thick images, spaced by 3 mm. Bilateral rotational multiplanar reformat images were created at each carotid terminus with a thickness of 7 mm and a spacing of 3 mm.

At our institution, patients with a known history of kidney disease receive Visipaque rather than Omnipaque if their calculated GFR is between 30 and 60 mL/min. Visipaque is also preferentially administered to patients without a history of renal impairment if their baseline creatinine result is not available at the time of contrast scanning. This practice is based on a randomized, controlled trial that showed lower rates of CIN when Visipaque was administered to patients with diabetes and chronic kidney disease compared with Omnipaque.[17] Prophylactic n-acetylcysteine or bolus intravenous fluid is not administered in the acute stroke setting. Although there is no specific hydration protocol, most patients receive intravenous fluids at rates of between 75 and 125 mL/h after contrast CT. The blood pressure of acute ischemic stroke patients who receive thrombolysis is maintained below 185/110 mm Hg to prevent hemorrhagic transformation of the infarct. For ischemic stroke patients who do not qualify for thrombolysis, blood pressure is not treated aggressively and allowed to ride up to 220/120 mm Hg to maintain cerebral perfusion pressure. Blood pressure is maintained under 160/90 mm Hg in hemorrhagic stroke patients without raised intracerebral pressures to prevent early expansion of the hematoma.

The main 2 outcomes recorded were as follows: the proportion of patients who developed CIN among those with adequately documented serial creatinine values within 72 hours and the proportion of patients who developed chronic kidney disease regardless of the availability of creatinine values within 72 hours.

For the present analysis, patients were included if they had a baseline creatinine value before contrast scanning and serial creatinine values recorded between baseline and 3 days and/or later creatinine results (day 4 and onward). Known risk factors for the development of CIN were identified through chart abstraction, including a documented history of chronic renal impairment and diabetes mellitus. For each patient, the total number and type of contrast studies performed within the first 24 hours was recorded, including CTA alone, CTA plus CTP, and/or digital subtraction angiography.

Calculations were performed by using the SAS (version 9.1; SAS Institute, Cary, NC) statistical software package. Results were expressed as the mean ± SD or median (range) for quantitative variables and as proportions for categoric findings. Unpaired t test, Wilcoxon rank sum test, or Fisher exact test was used to compare the differences between included and excluded, CIN and non-CIN, and Visipaque and Omnipaque patient groups. A power calculation by using PASS 2005 statistical software package (NCSS, Kaysville, Utah) was performed based on the number of patients with and without CIN. A probability of developing CIN of 15%–25% for diabetes and 20%–35% for history of chronic kidney disease was assumed based on previous publications.[15,18-20] The number of patients required to achieve 80% power to detect a 10% difference between the 2 groups by using a 2-sided binomial test ($\alpha = 0.05$; $P < .05$) was 186–194, assuming a 10% drop-out rate.

Results

A total of 331 patients presented to the emergency department with an acute stroke syndrome and had CTA and/or CTP imaging, and 198 met inclusion criteria of having sufficient creatinine levels available for analysis. The remainder were excluded because they did not have follow-up creatinine values available, because they were discharged, repatriated to another hospital after initial assessment, died, or blood work was not obtained.

There were no significant differences in baseline character-

Characteristics for the 5 patients who developed CIN

Characteristics	Patients Who Developed CIN				
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age, y	75	95	72	34	85
Gender	Female	Male	Female	Male	Female
Stroke type	Ischemic	Ischemic	Hemorrhagic	Hemorrhagic	Ischemic
Risk factors for CIN					
Known history of renal impairment	Yes*	Yes†	No	No	No
Diabetes	Yes	No	No	No	Yes
Type of contrast scan and number of scans within 24 hours	1 CTA+CTP	1 CTA+CTP	1 CTA	1 CTA	1 CTA+CTP
Creatinine level known at time of contrast CT?	Yes	Yes	Yes	Yes	No
GFR day 0, mL/min	46	42	66	166	64
GFR nadir, mL/min	32	29	52	132	43
Creatinine levels, μmol/L					
Day 0	132	102	54	66	92
Day 1	167	95	53	80	97
Day 2	189	85	60	81	133
Day 3	191	147	68	83	109
Type of contrast	Iso-osmolar	Low osmolar	Low osmolar	Low osmolar	Low osmolar
Outcome					
Chronic renal failure	No	No	No	No	No
Dialysis	No	No	No	No	No

Note:—CTA indicates CT angiography; CTP, CT perfusion; CIN, contrast-induced nephropathy; GFR, glomerular filtration rate.
* Diabetic nephropathy.
† Polycystic kidney disease.

istics (age, sex, and creatinine) between the study group and the excluded cohort of patients. Of the study cohort, mean age was 65.4 ± 18.9 years, 99 (50%) were female, and mean baseline creatinine was 88 μmol/L (compared with 53 female patients[47%], mean age of 68.7 ± 15.2 years, and mean baseline creatinine of 89 μmol/L in the excluded patients). A total of 134 ischemic stroke patients had a baseline CTA+CTP study, and 64 hemorrhagic stroke patients had a baseline CTA only. There were 10 patients (5%) with a known history of chronic kidney disease, and 22 (11%) patients with diabetes mellitus.

The presence or absence of CIN could be definitively assessed in 175 patients who had serial creatinine measurements within the first 72 hours. The median absolute change in creatinine from admission to day 3 was −12 mmol/L (range, −52 to 43 mmol/L). Five patients (2.9%) had a 25% or more increase in creatinine consistent with a diagnosis of CIN: 1 between days 0 and 1, 1 between days 0 and 2, and 3 between days 0 and 3.

The table describes the characteristics of the 5 patients who developed CIN. Patients 3-5 did not develop very severe CIN, as evidenced by their nadir GFRs that all measured 40 mL/min or more. Patients with CIN were more likely to have a history of renal impairment than those who did not develop CIN (P = .02). The relative risk of developing CIN with a history of renal impairment was 11 (95% confidence interval [CI] = 2.1–58.5). Diabetes mellitus was not found to be a significant risk factor for the development of CIN in this group (P = .1; 95% CI = 0.8–26.2). Importantly, none of the 5 patients with CIN required dialysis or developed chronic kidney disease.

In terms of the type of contrast agent used, 59 (34%) of 175 received Visipaque during the baseline scan, and only 1 of them (1.7%) developed CIN. The remainder received Omnipaque, and 4 of them (3.4%) developed CIN. Median baseline creatinine values in the Visipaque and Omnipaque groups

were 87 and 77 μmol/L, respectively (P = .016). The type of contrast agent did not affect the development of CIN (P = .66; risk ratio = 2.0; 95% CI = 0.2–17.8).

An additional 23 patients did not have serial creatinine measurements within the first 72 hours but did have later follow-up creatinine levels between days 3 and 5 and afterward (mean follow-up, 87 days). None of these patients had evidence of renal failure over this follow-up time period. The median change in creatinine for this group was −0.5 mmol/L (range, −13 to 13 mmol/L). Therefore, even if CIN had developed acutely in these patients, there does not appear to have been any long-term sequelae.

In a subgroup of 47 (27%) of 175 patients, the CTA and/or CTP study was performed before a baseline creatinine result was available. Only 1 (2%) of these 47 patients developed CIN, which was reversible. This patient had a history of diabetes.

CIN or chronic kidney disease was not observed in any patient who received higher than average doses of contrast administration. Of the 134 ischemic stroke patients, 49 (36.6%) had a repeat CTA+CTP scan within 24 hours of the initial CTA+CTP study, corresponding with a total of 260 mL of injected contrast medium. Similarly, 2 patients (1.5%) had an additional CTA study within 24 hours of the baseline CTA+CTP study, corresponding with a total of 220 mL of contrast medium. Three patients (2.2%) received a digital subtraction cerebral angiogram within 24 hours of baseline CTA+CTP, corresponding with a total of approximately 280–330 mL of injected contrast medium. One unstable ischemic stroke patient received 2 CTA studies and 1 cerebral angiogram within 24 hours of the original CTA+CTP study. None of these patients with additional contrast studies developed CIN or chronic kidney disease despite the higher volumes of contrast used. Similarly, of 64 hemorrhagic stroke patients, 4 (6.2%) had an additional CTA study within 24 hours of the baseline study, corresponding with a total 180 mL of injected

contrast medium. Eighteen patients (28.1%) received a cerebral angiogram within 24 hours of the CTA examination. None of these patients developed CIN or chronic kidney disease, despite the higher contrast loads.

The mean total contrast volume administered within 24 hours to the 5 patients with CIN was 114 mL (SD, ±21.9 mL), whereas the total mean contrast volume administered within 24 hours to the 170 non-CIN patients was 174 mL (SD, ±73.2 mL). We did not detect a dose-dependent risk of CIN ($P = .1$).

Discussion

Emergent diagnostic evaluation is critical in the management of acute stroke. CTA/CTP studies are increasingly available to assist in acute stroke evaluation. The impact of the information provided by these imaging modalities on stroke outcome is under investigation. It is not yet clear whether these investigations are sufficiently safe to warrant their widespread use. This study shows that the overall incidence of CIN in an acute stroke patient cohort with no known history of renal dysfunction is relatively low, at less than 3%. Of importance, none of these cases of CIN required dialysis or progressed to renal failure.

The rate of CIN reported in nonstroke patient cohorts that included patients with pre-existing renal dysfunction or diabetes mellitus, in which a standard prehydration protocol was not administered, has been between 12% and 26%.[18,21,22] However, many of the studies that showed an unacceptably high incidence of CIN leading to mortality and morbidity in hospitalized patients included patients with advanced renal disease (GFR, <30 mL/min), cardiogenic shock, volume depletion, and poor cardiac output after myocardial infarction.[15,20] The low incidence of CIN observed in the present study is comparable with that of a recent study that also assessed the effects of contrast administration in stroke patients exclusively.[23] This study showed an overall CIN incidence of 3% in acute stroke patients undergoing emergent CTA. Two previous studies that also focused on contrast-enhanced stroke imaging demonstrated a much lower incidence of renal failure due to CIN (0.37%[24] and 0%[25]). However, these studies only assessed the baseline, maximum, and discharge or 1-week levels, as well as the first, maximum, and discharge creatinine levels, respectively. They did not record serial creatinine levels within an early defined time period. Although they were able to identify chronic kidney disease, the broad timeframe of the creatinine measurements in these other studies makes them less sensitive in identifying CIN and also makes them less reliably able to attribute creatinine rises to contrast administration.

Multiple predisposing risk factors for the development of CIN have been identified previously.[12,18,19] The most important predictor of CIN is a history of chronic kidney disease, with a reported incidence of up to 50% in patients with advanced chronic kidney disease. The second most important predictor is thought to be diabetes mellitus, mostly attributable to diabetic nephropathy.[12] Some previous studies have also suggested a dose-dependent risk of CIN with higher volumes of contrast administered,[15,20,26] but others have not.[19] Although we confirmed that a history of renal impairment increases the likelihood of developing CIN, we could not detect a similar relationship for a history of diabetes mellitus

despite the adequate power of the study as outlined in the Materials and Methods section.

There was no apparent relationship between the volume of contrast agent administered and CIN. However, the power analysis to determine the adequacy of this study to rule out such a relationship could not be reliably performed. This was because estimates in the literature of the probability of developing CIN in relation to contrast volume were coarse and inconsistent. Furthermore, the use of high and low osmolar contrast agents in the literature was varied and not directly comparable with our own study. Without such a reliable starting probability, power calculation would not be valid. It is worth noting that the mean contrast volume of the patients who developed CIN was lower than that of patients who did not develop CIN. Therefore, it is not probable that there is a dose-dependent relationship between contrast volume and CIN. Studies that have identified a positive correlation between diabetes mellitus and contrast volume with the development of CIN included more patients with significant diabetic nephropathy and patients with a greater mean age and/or a GFR of 30 mL/min or less.[15,20]

The exclusive use of lower-risk contrast agents (low osmolar and iso-osmolar agents) at our institution may have helped to minimize the risk of CIN in our population. The use of nonionic low osmolar contrast agents has been shown to be less nephrotoxic in patients with known chronic kidney disease compared with high osmolar contrast agents.[27] Between low and iso-osmolar contrast agents, our study did not show a significant difference in the risk of developing CIN. To date, one randomized trial has directly compared low osmolar (Omnipaque) and iso-osmolar (Visipaque) contrast agents.[17] In that study, diabetic patients with chronic kidney disease undergoing coronary angiography had a statistically significant lower incidence of CIN when an iso-osmolar agent was used versus a low osmolar agent (3% versus 26%; $P = .002$).

Treatment delays have been associated with worse functional outcomes in stroke survivors.[28,29] In a subset of patients in this study with no history of renal impairment, contrast agent was administered before the availability of a baseline creatinine value. The incidence of CIN was low (2%) in these patients. Therefore, in this subset, it may not be necessary to delay or defer contrast CT if a creatinine value is not immediately available.

Because contrast CT studies are usually obtained within 25 minutes of the patient's arrival to the emergency department, it is not feasible to use the usual recommended measures intended to prevent the development of CIN in the acute stroke setting. These include intravenous prehydration for 12 hours, intravenous *n*-acetylcysteine (2 doses, 12 hours apart before the contrast study), or a 1-hour intravenous sodium bicarbonate infusion before the administration of contrast medium.[11] The finding that none of the patients in this study developed chronic renal impairment and few developed CIN demonstrates the relative safety of intravenous contrast administration even in the absence of these measures.

There are limitations of this study not noted above that are inherent to its retrospective nature. A substantial number of patients were excluded due to repatriation, death, or the lack of adequate creatinine values. Therefore, the true incidence of CIN and/or chronic kidney disease may have been underesti-

mated or overestimated. Although there were no cases of CIN in this study that led to chronic kidney disease, we cannot reliably estimate the risk of such an occurrence due to the low number of CIN cases. In addition, whereas this study was adequate to assess the likelihood of a history of diabetes mellitus and chronic kidney disease in patients with CIN, this adequacy was based on a power estimate. For such a retrospective study, an even greater number of patients would improve the overall reliability of the findings.

Conclusions

This study estimates the renal safety of emergent contrast-enhanced CT imaging in acute stroke patients, when patients without an available serum creatinine are screened for a history of chronic kidney disease and patients with advanced kidney disease (GFR, <30 mL/min) are excluded. The potential for developing long-term renal sequelae is negligible, even when renoprotective preventative measures are not implemented. Taken together with other studies, our findings can help to reassure clinicians that, if indicated, CTA/CTP can be safely applied as part of acute stroke imaging protocols.

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