PATIENT SAFETY

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Prolonged Carotid Sinus Reflex Is a Risk Factor for Contrast-Induced Nephropathy following Carotid Artery Stenting

BACKGROUND AND PURPOSE: Although many studies have demonstrated that CIN is associated with in-hospital and long-term mortality, the incidence of CIN following CAS is unclear. We investigated the incidence of CIN, defined as an increase from a baseline creatinine value of at least 0.5 mg/dL or 25% within 72 hours of contrast administration, and we also examined renal function in the late phase after CAS.

MATERIALS AND METHODS: We examined 80 patients who underwent CAS between April 2005 and December 2009. Clinical background, laboratory data, contrast volume, and clinical course were collected and analyzed.

RESULTS: The incidence of CIN was 8.8% (7/80), and no patients required hemodialysis. In the group that developed CIN, prolonged CSR after CAS was found in 57.1% (4/7) of cases; this incidence differed significantly ($P = .001$) from that in the group without development of CIN. Neither preoperative renal function, contrast volume, nor history was related to the incidence of CIN, while on multivariate analysis, prolonged CSR was found to be an independent risk factor for CIN. The incidence of elevation in creatinine values at 6 months after CAS was 8.2% (6/73). All patients who developed delayed renal impairment had pre-existing CKD; this finding differed significantly ($P = .04$) from that in the group without development of delayed renal impairment.

CONCLUSIONS: Because patients who develop prolonged CSR after CAS are at increased risk of perioperative major adverse clinical events including CIN, patients at high risk for this condition should be carefully managed to prevent increased morbidity and mortality.

ABBREVIATIONS: CAD = coronary artery disease; CAS = carotid artery stenting; CEA = carotid endarterectomy; CI = confidence interval; CIN = contrast-induced nephropathy; CKD = chronic kidney disease; CSR = carotid sinus reflex; CTA = CT angiography; CTP = CT perfusion; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate; HTN = hypertension; ICS = internal carotid stenosis; OR = odds ratio; PCI = percutaneous coronary intervention; Read. = re-administration; RI = renal impairment; SCr = serum creatinine; SPSS = Statistical Package for the Social Sciences

Although CIN was previously believed to be characterized by a transient and asymptomatic increase in SCr levels, many studies have demonstrated that it is associated with in-hospital and long-term mortality.¹⁻⁴ The incidence of CIN is low (1%–2%) in the general population; however, in high-risk patients, it has been calculated to be >20%–30%.⁵⁻⁷ Several risk factors for CIN have been described, including CKD, diabetes mellitus, hypertension, older age, use of nephrotoxic medications, large contrast volume, dehydration, and repeated exposure to contrast agents (<72 hours).^{1,8-11} CIN has also been linked to length of hospital stay and increased hospital resource use.³ Because there is no effective treatment once renal injury has occurred, prevention is recommended for all patients at risk for CIN.

Hemodynamic depression after both CEA and CAS is caused by the manipulation of the carotid sinus. The frequency of development of prolonged CSR following CAS procedures varies from

11% to 42%, and plaque characteristics and anatomic risk factors associated with such hemodynamic depression include calcified plaque, fibrous plaque, eccentric plaque, lesions involving the carotid bulb, presence of contralateral stenosis or occlusion, length of stenosis, right-sided lesions, and balloon-to-artery ratio.¹²⁻¹⁶ The clinical efficacy of CEA was established in clinical trials for symptomatic and asymptomatic carotid occlusive disease.^{17,18} CAS has been recommended as a less invasive but potentially equally effective treatment for carotid disease.¹⁹ Because of the association of arterial hypertension, cigarette smoking, diabetes mellitus, and dyslipidemia with carotid occlusive disease, monitoring is required for CIN in patients undergoing CAS.

The most commonly used definition of CIN is an increase from a baseline SCr level of at least 0.5 mg/dL or 25% within 48–72 hours after exposure to contrast agent. SCr level peaks between 2 and 5 days after contrast exposure and, in general, returns to baseline within 2 weeks.^{5,20} Because the incidence of and risk factors for CIN and the change of SCr values at 6 months after CAS are unknown, we examined renal function in both the acute and late phases.

Materials and Methods

Between April 2005 and December 2009, all patients admitted with a diagnosis of ICS and treated with CAS in our local department of

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neurosurgery at the National Hospital Organization Toyohashi Medical Center were reviewed in a retrospective analysis. Background risk factors for CIN (age, history of hypertension, diabetes mellitus and CAD, use of diuretics, contrast volume, and re-administration of contrast agent within 72 hours) and preoperative SCr values were collected. Following CAS procedures, we collected SCr values within 72 hours as acute phase values and at 6 months after CAS as the late phase values. In addition, to estimate GFR, we used the new Japanese coefficient $194 \times \text{SCr}^{-1.094} \times \text{age in years}^{-0.287} (\times 0.739, \text{ if female})$.²¹

CAS was performed by using our standard procedure with the patient under local anesthesia. We evaluated preoperative carotid plaque by using sonography, CTA, black-blood MR imaging, and, if necessary, virtual histology intravascular sonography.²² All patients were premedicated with dual antiplatelet agents (aspirin and/or clopidogrel and/or cilostazol) and administered fluid infusion at a rate of 1 mL/kg/h for 6 hours before the procedure. An intravenous heparin bolus of 100 IU/kg of weight was administered after 8F-sheath insertion, and atropine was routinely administered before angioplasty. If required, vasopressor was used intraoperatively for bolus administration. The standard CAS procedure involved the following: placement of a protective device, pre-stent angioplasty, placement with a self-expandable type of stent, and post-stent angioplasty. In cases of mild stenosis (50%–70%), pre-stent angioplasty was often abbreviated. Pre-stent angioplasty was usually performed by using a 3.0–4.0 × 30–40 mm angioplasty balloon and post-stent angioplasty by using a 4.0–5.0 × 20–40 mm angioplasty balloon.

All patients were continuously administered anticoagulant and fluid infusion at a rate of 1 mL/kg/h for 24–48 hours after the procedure. In the stroke care unit, the vital signs, urinary volume, and neurologic signs were monitored; additionally any causes of hemodynamic depression and elevated SCr value were also monitored. We defined prolonged CSR as a sustained low systolic blood pressure of <80 mm Hg for 30 minutes or new neurologic signs caused by a >30% decrease in baseline systolic blood pressure. Continuous administration of vasopressor was started if prolonged CSR occurred. We examined patients with prolonged CSR.

All patients received the nonionic low-osmolar contrast agent iohexol (Omnipaque 300; Daiichi-Sankyo, Tokyo, Japan) during the CAS procedure. A few patients underwent CTA within 72 hours before CAS and were administered the nonionic low-osmolar contrast agent iopamidol (Iopamiron 300; Bayer Healthcare, Osaka, Japan). Some patients underwent coronary angiography simultaneously by using the nonionic low-osmolar contrast agent iohexol (Omnipaque 350; Daiichi-Sankyo). Contrast agent volume was also determined in cases in which coronary angiography was performed simultaneously. For each patient, we calculated the maximum contrast volume with the formula $(5 \times \text{body weight [kilograms]})$ divided by the SCr value (milligrams per deciliter).²³ From this contrast limit, we determined the contrast ratio by dividing administered contrast volume by the calculated maximum volume. Each contrast volume administered in a CAS procedure was determined by reference to preoperative eGFR and the contrast ratio.

Values are presented as the mean ± SD. Categorical variables were analyzed by the χ^2 or Fisher exact test, as appropriate. Continuous variables with normal distributions were analyzed by the Student *t* test, and those with nonnormal distributions, by the Mann-Whitney *U* test. Univariate and multivariate analyses were performed to determine which factors correlated with the development of CIN. *P* values < .05 were considered significant. All statistical analyses were performed by using Dr. SPSS II (SPSS Japan, Tokyo, Japan).

Table 1: Baseline characteristics and univariate analysis of development of CIN

	All	CIN (<i>n</i> = 7, 8.8%)	No CIN (<i>n</i> = 73, 91.2%)	<i>P</i> Value
Age (yr)	73.7	75.1	73.6	.60
Pre-SCr	1.11	0.99	1.12	.67
Post-SCr	1.16	1.39	1.14	.15
Pre-eGFR	55.6	60.8	55.1	.44
Pre-eGFR <60	60.0%	42.9%	61.6%	.43
HTN	71.3%	85.7%	69.9%	.67
DM	37.5%	14.3%	39.7%	.25
CAD	50.0%	28.6%	52.1%	.43
Diuretic	10.0%	0%	11.0%	1.00
Prolonged CSR	10.0%	57.1%	5.5%	.001 ^a
Re-administration	3.4%	14.3%	2.7%	.24
Contrast volume	147.3 mL	148.6 mL	147.2 mL	.86
Contrast ratio	0.57	0.49	0.58	.66

^a *P* < .001 on multivariate analysis (OR, 23.0; 95% CI, 3.8–143).

Results

A total of 101 consecutive patients who underwent CAS during the study period were included. Twenty patients were excluded due to lack of creatinine values on short-term follow-up, and 1 patient was excluded due to the need for continued hemodialysis. Eighty patients were therefore included. There were 10 (12.5%) female patients, and the mean age of all patients was 73.7 ± 7.6 years (range, 57–92 years). There were 57 (71.3%) patients with hypertension, 30 (37.5%) patients with diabetes mellitus, 40 (50.0%) patients with CAD, and 8 (10.0%) patients on diuretic agents. The baseline SCr value and eGFR were 1.11 ± 0.47 mg/dL and 55.6 ± 18.6 mL/min/1.73 m², respectively, with an eGFR below 60 mL/min/1.73 m² in 48 (60.0%) patients. The mean amount of contrast administered and mean contrast ratio were 147.3 ± 48.3 mL and 0.57 ± 0.32 , respectively. Three (3.4%) patients underwent repeat administration of contrast agent within 72 hours, and coronary angiography was simultaneously performed in 14 (17.5%) patients. The technical success rate of CAS with embolic protective device was 100%. Postoperative prolonged CSR was found in 8 patients (10.0%), all of whom recovered within a few days with use of continuous intravenous catecholamine infusion. No patients developed infection, dehydration, or anuria; required transcatheter or transvenous pacing; or required hemodialysis postoperatively.

The incidence of CIN was 8.8% (7/80), and the 2 groups were comparable with regard to clinical features, as shown in Tables 1 and 2. Prolonged CSR after CAS was found in 4 (57.1%) of 7 patients who developed CIN but in only 4 (5.5%) of 73 patients who did not develop CIN, and there was a significant difference (*P* = .001) in the presence of poststenting prolonged CSR between the 2 groups. Neither preoperative renal function, amount of contrast agent, nor history was related to the incidence of CIN. Only variables with a value of *P* < .25 on univariate analysis were included in the multivariate model. Prolonged CSR was found to be an independent risk factor for CIN (OR, 23.0; 95% CI, 3.8–143; *P* < .001).

Because for 7 patients a follow-up SCr value at 6 months after CAS could not be obtained due to transfer to another hospital or death (pneumonia and ruptured abdominal aortic aneurysm), 73 patients were included in the assessment of renal function in the late phase. An elevation of SCr of >0.5

Table 2: Summary in patients with CIN

Patient No.	Age (yr)/Sex	Pre-SCr	Post-SCr	Pre-eGFR	HTN	DM	CAD	Diuretic	Prolonged CSR	Read.	Contrast Volume (mL)	Contrast Ratio
1	65/M	1.32	2.12	43.2	+	–	+	–	+	–	200	0.78
2	75/M	0.69	0.88	84.3	+	–	–	–	+	–	190	0.45
3	74/M	0.82	1.06	70.1	–	+	–	–	–	+	175	0.45
4	76/M	1.25	1.79	43.9	+	–	–	–	–	–	190	0.72
5	84/M	1.24	1.65	43.0	+	–	–	–	–	–	90	0.46
6	73/M	0.92	1.33	62.0	+	–	–	–	+	–	100	0.38
7	79/M	0.72	0.91	79.3	+	–	+	–	+	–	95	0.21

Table 3: Univariate analysis of development of delayed renal impairment

	Delayed RI (+) (n = 6, 8.2%)	Delayed RI (–) (n = 67, 91.8%)	P Value
Age (yr)	72.0	73.3	.68
Pre-SCr	1.16	1.05	.10
Post-SCr	1.31	1.11	.09
SCr (6 mo)	1.88	1.03	<.001
Pre-eGFR	48.9	57.3	.27
Pre-eGFR <60	100%	55.2%	.04
HTN	83.3%	73.1%	.21
DM	33.3%	40.3%	.17
CAD	50.0%	47.8%	1.00
Diuretic	0%	10.4%	.46
Re-administration	0%	4.5%	.26
Contrast volume	171.7 mL	145.3 mL	.26
Contrast ratio	0.64	0.53	.20
CIN	16.7%	9.0%	.43

Table 4: SCr value and eGFR in patients with delayed renal impairment

Patient No.	Pre-SCr	Post-SCr	SCr (6 mo)	Pre-eGFR	CIN
1	1.32	2.12	2.68	43.2	+
2	1.30	1.34	1.82	43.9	–
3	1.20	1.25	1.53	45.2	–
4	1.16	1.10	2.46	48.7	–
5	1.00	0.97	1.38	55.6	–
6	0.99	1.09	1.43	57.0	–

mg/dL or >25% was found in 6 patients (8.2%) at 6 months after CAS. Of these 6 patients, only 1 developed CIN at the acute phase, while the other 5 patients had SCr values within the normal range. The baseline SCr value and eGFR were 1.16 mg/dL and 48.9 mL/min/1.73 m², respectively, while at 6 months after CAS, they were 1.88 mg/dL and 30.6 mL/min/1.73 m², respectively, with both exhibiting significant deterioration ($P = .002$). The baseline eGFR values of the 6 patients who developed delayed renal impairment were all below 60 mL/min/1.73 m², whereas the incidence of eGFR < 60 was 55.2% (37/67) in the healthy group; this difference was significant ($P = .04$, Table 3). Any other factors such as history, development of CIN, and contrast volume were not related to the occurrence of delayed renal impairment. On multivariate analysis, no factor was found to be independent. In patients with development of delayed renal impairment, the changes in SCr values and eGFR following CAS are shown in Table 4.

Discussion

To our knowledge, this study is the first to have investigated renal function in both the acute and late phases after CAS. While CIN has been reported to occur mainly in association with coronary procedures, several studies have described the incidence of CIN after CTA, CTP, and catheter intervention in patients with stroke.^{24–30} CIN occurred in 3% of cases (7/224) within 5 days in patients with acute stroke syndrome who underwent CTA within 24 hours from the onset of symptoms.²⁴ With the use of CTA and CTP to guide emergency management of acute stroke, CIN occurred in 2.9% of 175 patients within 72 hours.²⁶ In our study, CIN developed in 8.8% of patients, a rate higher than that in these reports, despite adequate fluid replacement beginning preoperatively to prevent renal sequelae. Previously, the risk of CIN may have been higher after intra-arterial than intravenous contrast agent injection.^{31,32} However, none of these studies provide any consideration of the administration process in contemporary practice, especially with regard to CTA, in which a comparatively large volume of contrast agent may be given as a compact intravenous bolus rather than an infusion.³³ Because patients with ICS also have cardiac, metabolic, and renal complications, we thought they may more easily develop CIN, regardless of the route of administration.

In a recent study, the incidence of hypotension was 28% and administration of either vasopressor or anticholinergic drugs was 48% during the 12 hours after CAS and extended hospitalization for >1 night due to prolonged CSR was 9%.³⁴ With detailed multimodal preoperative assessment and careful determination of angioplasty balloon size, the incidence of prolonged hypotension could be suppressed 10% (8/80) in our study, compared with other studies.^{12,13,15,35,36} Once prolonged CSR occurred, continuous intravenous vasopressor infusion was immediately administered with monitoring of vital signs, urine output, and neurologic signs and symptoms. Despite the prevention of excessive hypotension and the maintenance of sufficient urine output, prolonged CSR was an independent risk factor for CIN. Patients who develop persistent hemodynamic depression after CAS are at increased risk of periprocedural major adverse clinical events and stroke.¹⁴ Patients at high risk for prolonged CSR should thus be carefully managed and precautions should be taken to prevent increased morbidity and mortality.

Principally 2 pathogenetic mechanisms, direct cytotoxicity of contrast agents and ischemic injury, have been implicated in the development of CIN.³⁷ McCullough³³ reported that after contrast enters the renal vasculature, the release of adenosine, endothelin, and prostaglandin dysregulation causes in-

trarenal vasoconstriction, and there is an overall –50% sustained reduction in renal blood flow lasting for several hours. The stasis of contrast allows direct cellular injury and death to renal tubular cells, and the degree of cytotoxicity to renal tubular cells is related to the length of contrast exposure. The sustained reduction in renal blood flow to the outer medulla leads to medullary hypoxia, ischemic injury, and death of renal tubular cells. In addition, any superimposed insult such as sustained hypotension, microshowers of atheroembolic material during catheter intervention, the use of intra-aortic balloon pumping, or a bleeding complication can amplify the injury processes occurring in the kidney. We considered that prolonged CSR increases the possibility of developing CIN due to the reduction of renal blood flow in relation to faint systemic hypotension.

The incidence of increase of >0.5 mg/dL or >25% from baseline at 1 month was 12.5% (16/126) in patients with chronic renal insufficiency undergoing coronary angiography or intervention.³⁸ In the late phase (>30 days), 9 of 68 (13%) patients with acute stroke had a >25% rise in SCr levels compared with baseline SCr values following CTA.²⁴ Our finding of delayed renal impairment in 8.2% of patients (6/73) at 6 months after CAS was also in agreement with that in these previous reports. Although CIN occurred in 7 patients, only 1 developed delayed renal impairment. Krol et al²⁴ reported that a late rise in SCr level may not have been solely due to the contrast use; many factors such as dehydration, drugs, and hemodynamic complications might have contributed to a late increase in SCr level. All patients who exhibited delayed renal impairment had a preoperative decrease in eGFR (moderate or more in CKD stage III), so there is an increased probability that renal disease had progressed due to new or worsening medical conditions rather than contrast exposure.

Many studies have shown that the volume of contrast agent is a risk factor for CIN. The mean contrast volume is higher in patients with CIN, and most multivariate analyses have shown that absolute contrast volume is an independent predictor of CIN.^{1,9,11,39} Cigarroa et al²³ defined maximum contrast volume as (5 × body weight [kilograms]) divided by SCr (milligrams/deciliter). Exceeding this maximum contrast volume was the strongest independent predictor of nephropathy requiring dialysis after PCI.⁹ In patients following primary PCI, development of CIN was associated with both absolute contrast volume and contrast ratio, and patients whose contrast ratio was >1 showed a more complicated in-hospital clinical course and higher mortality.⁴⁰ Our findings could not obtain a statistically significant difference in either contrast volume or contrast ratio in the incidence of CIN, probably because of the small sample size.

The limitations of this study are its retrospective nature and the lack of a control group. A few studies have compared the incidence of CIN in patients with acute stroke with a control group following contrast-enhanced CT.^{28,29} To determine the true incidence of CIN in patients with ICS, it will be necessary to investigate patients after diagnostic angiography or CTA without CAS. In patients at high risk for CIN, the frequency in use and amount of contrast agent should be as low as possible; in the future, a non-nephrotoxic drug should be required.

Conclusions

This study found that the incidence of CIN was 8.8% following CAS and that prolonged CSR was an independent risk factor for CIN. Additionally, the incidence of delayed renal impairment was 8.2%, and all patients who developed delayed renal impairment had pre-existing renal impairment (CKD stage III or more). To prevent CIN, one should understand which case tends to cause prolonged CSR; in other words, avoiding prolonged CSR leads to preventing CIN.

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