—**Original**—

Incidence and Clinical Significance of Ischemic Stroke Following Cardiac Catheterization

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Background: Ischemic stroke (IS) is one of the most serious complications after cardiac catheterization. This study aimed to investigate the incidence of IS in patients undergoing cardiac catheterization as well as the risk factors and neurological prognosis of IS.

Methods: We retrospectively analyzed the data of consecutive 2,848 patients (age 69.1 ± 11.1 years, 2,118 men) who underwent cardiac catheterization from January 2011 to December 2013 to determine the incidence and clinical outcomes of IS.

Results: Thirteen patients (0.46%) developed IS after cardiac catheterization, necessitating treatment in the stroke care unit. Multivariate analysis identified five unmodifiable risk factors (age, atrial fibrillation, current smoking, prior stroke, and prior coronary artery bypass graft surgery) and two modifiable risk factors (additional internal thoracic artery angiography and the transbrachial approach) associated with IS. The initial National Institutes of Health Stroke Scale score was 6.9 ± 9.3 at the onset of IS, which improved to 3.1 ± 8.2 at the time of discharge. Five patients demonstrated complete recovery at discharge (modified Rankin Scale [mRS] score = 0), seven demonstrated residual neurological deficit (mRS = 2.7 ± 1.7, including two cases of severe deficit), and one patient died in hospital (mRS = 6).

Conclusions: Although rare, IS following cardiac catheterization is associated with significant morbidity and mortality. Avoiding unnecessary internal thoracic artery angiography and the brachial approach may reduce the incidence, and appropriate use of anticoagulants or thrombolytics may improve the prognosis and decrease residual neurological deficits. (J Nippon Med Sch 2025; 92: 360–367)

Key words: ischemic stroke, cardiac catheterization, risk factor, The National Institutes of Health Stroke Scale score, modified Rankin Scale

Introduction

Ischemic stroke (IS) is one of the most serious complications of cardiac catheterization because it causes prolonged hospitalization, neurological sequelae, and even in-hospital death[1–5]. Although several studies have assessed the incidence of and risk factors for this condition[6–9], no definitive prophylactic treatment strategy has yet been established. Clinicians need to have a thorough understanding of the modifiable risk factors for IS that can be optimally managed before and during cardiac catheterization.

Most previous studies on IS after cardiac catheterization focused on the process before the onset of IS[6,7]. Few studies have investigated the neurological prognosis, treatment methods, or causal relationship between IS and cardiac catheterization after the onset of IS[10] to provide a better insight into the clinical significance of this condition. Furthermore, no definitive treatment strategy has

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been established for the management of IS after cardiac catheterization. Therefore, it is important to identify an optimal treatment method and study its outcomes.

In this study, we aimed to identify 1) the incidence of IS in patients undergoing cardiac catheterization, 2) unmodifiable and modifiable risk factors for IS after cardiac catheterization, 3) neurological prognosis after the onset of IS, and 4) an optimal treatment strategy for the management of IS and its outcomes.

Materials and Methods

Study Population

We retrospectively investigated 3,031 consecutive patients who underwent cardiac catheterization at Nippon Medical School Hospital between January 2011 and December 2013. After excluding catheterizations involving endovascular therapy and electrophysiological studies pertaining to catheter ablation, 2,848 patients were included in this study. Patients were classified into two groups according to the presence or absence of post-catheterization IS that required treatment in the stroke care unit. Patients' clinical characteristics, procedural findings, and in-hospital clinical outcomes were obtained from medical records and compared between the patients with and without IS.

The Medical Ethics Committee of Nippon Medical School Hospital reviewed and approved this clinical study (approval number: B-2024-877). Due to the retrospective design of our study, we used an opt-out consent method by posting the research information in our hospital instead of obtaining informed consent from each patient.

Definition of Ischemic Stroke

IS was defined as a transient or permanent new neurological deficit that occurred within 24 hours after a cardiac catheterization procedure without any evidence of a hemorrhagic stroke. Cerebrovascular events were diagnosed by experienced neurologists at our hospital based on both the clinical findings, such as the sudden or rapid onset of new focal neurological signs, and radiological findings of imaging studies such as computed tomography (CT) and/or magnetic resonance imaging (MRI). Brain MRI was used to identify recent cerebral ischemic injury, the diagnostic criterion being the presence of a new hyperintense lesion on the scan. Brain CT was used to confirm a delayed clinical diagnosis of stroke after cardiac catheterization. The neurologists also treated the acute phase of IS in patients who presented with this complication.

Neurological Assessment

The National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS) were used for quantitative neurological assessment. The NIHSS is used to determine the severity of a stroke. It is a 15-item tool that assesses the level of consciousness, visual field, eye movements, facial paralysis, motor ataxia, sensory disorder, and aphasia, among others, with scores ranging from 0 to 42 points[10]. The mRS is used to determine the severity of neurological outcomes of stroke in the chronic phase. As noted with the NIHSS score, the higher the mRS score, the greater the degree of severity/disability following stroke. The mRS scores range from 0 to 6 points[11]. The NIHSS and mRS are commonly used by neurologists to assess stroke severity[12]. In this study, we used both scales at the onset of stroke and at the time of discharge.

Statistical Analysis

Continuous variables are expressed as means ± standard deviation (SD), while categorical variables are expressed as percentages (%). The Student's t-test was used to assess the statistical significance of continuous variables and Fisher's exact test was used to analyze categorical variables. Univariate and multivariate logistic regression analyses were performed to identify risk factors for procedure-related ischemic stroke. In the multivariate analysis, risk factors included age, sex, atrial fibrillation, current smoking, prior myocardial infarction, prior coronary artery bypass grafting, prior stroke, cilostazol use, additional internal thoracic artery angiography, and the brachial approach. We used two models for the multivariate analysis because there was a significant correlation between prior coronary artery bypass grafting and additional internal thoracic angiography. All statistical analyses were performed with SPSS software version 28 (IBM, Somers, New York, USA). Statistical significance was set at $p < 0.05$.

Results

Baseline Patient Characteristics and Procedure Characteristics with or without IS

Among the 2,848 patients, diagnostic cardiac catheterization and therapeutic catheter intervention were performed in 1,927 and 921 patients, respectively. Additional internal thoracic artery (ITA) angiography was performed in 301 patients. Coronary angiography (CAG) revealed that 1,221 patients had multivessel disease and 1,627 patients had single-vessel disease or no significant stenosis. Regarding the catheterization approach sites, the

Table 1 Baseline characteristics of patients with and without catheterization procedure-related ischemic stroke

	Procedure-related ischemic stroke (n = 13)	No ischemic stroke (n = 2,835)	p value
Age (y, mean ± SD)	75.9 ± 9.1	69.0 ± 11.2	0.031
Sex (men)	9 (69.2%)	2,109 (74.4%)	0.276
Hypertension	12 (92.3%)	2,301 (81.2%)	0.202
Diabetes mellitus	4 (30.8%)	1,122 (39.6%)	0.619
Dyslipidemia	9 (69.2%)	1,860 (65.6%)	0.663
Atrial fibrillation	5 (38.5%)	255 (9.0%)	<0.001
CKD	2 (15.4%)	393 (13.9%)	0.874
Current smoking	9 (69.2%)	542 (19.1%)	<0.001
Prior MI	7 (53.8%)	519 (18.3%)	0.001
Prior CABG	3 (23.1%)	210 (7.4%)	0.022
Prior stroke	6 (46.2%)	193 (6.8%)	<0.001
Peripheral artery disease	2 (15.4%)	324 (11.4%)	0.655
Aspirin	9 (69.2%)	1,829 (64.5%)	0.601
Clopidogrel	2 (15.4%)	736 (26.0%)	0.385
Cilostazol	3 (23.1%)	155 (5.5%)	0.005
Warfarin	1 (7.7%)	218 (7.7%)	0.961
Catheterization procedure			
CAG only	5 (38.5%)	1,621 (57.2%)	0.174
CAG + ITA angiography	5 (38.4%)	296 (10.4%)	0.001
PCI	3 (23.0%)	918 (32.4%)	0.474
Access site			
Upper extremity approach	9 (69.2%)	1,605 (56.6%)	0.360
Radial	6 (46.1%)	1,443 (50.9%)	0.733
Brachial	3 (23.1%)	162 (5.7%)	0.007
Femoral approach	4 (30.8%)	1,154 (40.7%)	0.467
Multiple access sites			
RA+FA	0	8 (0.28%)	0.848
BA+FA	0	6 (0.21%)	0.868
CAG findings			
Multivessel disease	9 (69.2%)	1,212 (42.7%)	0.054
Fluoroscopic time (min, mean ± SD)	28.6 ± 19.3	39.9 ± 178.3	0.819
Contrast volume (mL, mean ± SD)	107.8 ± 64.5	97.7 ± 55.8	0.844

BA: brachial approach, CABG: coronary artery bypass grafting, CAG: coronary angiography, CKD: chronic kidney disease, FA: femoral approach, ITA: internal thoracic artery, MI: myocardial infarction, PCI: percutaneous coronary intervention, RA: radial approach, SD: standard deviation

upper extremity approach was used in 1,614 cases (56.7%), including the radial approach in 1,449 cases (50.9%) and brachial approach in 165 cases (5.8%), while the femoral approach was used in 1,158 cases (40.7%). Multiple access sites were used in 14 patients (radial and femoral approach in eight cases, and brachial and femoral approach in six cases). Information about the access site was lacking for 62 patients. IS was observed in 13 (0.46%) patients. In terms of the severity of neurological deficits, transient neurological deficits occurred in five patients and permanent neurological deficits occurred in eight patients. IS was diagnosed based on the findings of both MRI and CT in seven patients, CT alone in four, and MRI alone in two patients.

Baseline patient and procedural characteristics are presented in **Table 1**. Compared to patients without IS, patients with IS were significantly older (75.9 ± 9.1 years vs. 69.0 ± 11.2, $p = 0.031$), had higher rates of atrial fibrillation (AF) (38.5% vs. 9.0%, $p < 0.001$), a higher proportion of current smokers (69.2% vs. 19.1%, $p < 0.001$), and higher rates of prior myocardial infarction (MI) (53.8% vs. 18.3%, $p = 0.001$), prior coronary artery bypass graft (CABG) procedures (23.1% vs. 7.4%, $p = 0.022$), and prior stroke (46.2% vs. 6.8%, $p < 0.001$). Patients with IS were prescribed cilostazol more frequently than those without IS (23.1% vs. 5.5%, $p = 0.005$). The incidence of concomi-

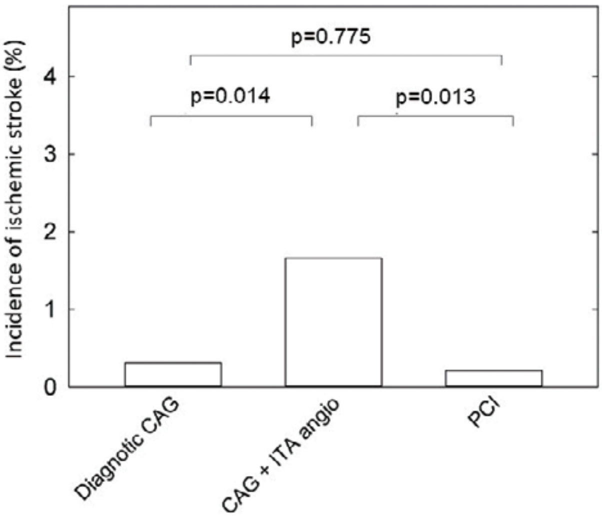

Fig. 1 Incidence of ischemic stroke after diagnostic coronary angiography (CAG), concomitant CAG and internal thoracic artery (ITA) angiography, and percutaneoouos coronary intervention (PCI). Ischemic stroke was defined as the presence of a newly appeared neurological deficit with ischemic findings observed during magnetic resonance imaging (MRI) and requiring management in a stroke care unit, as determined by an expert neurologist.

tant CAG and ITA angiography was significantly higher in patients with IS than in those without IS (38.4% vs. 10.4%, p = 0.001). IS occurred after diagnostic CAG, CAG concomitant with ITA angiography, and percutaneous coronary intervention (PCI) in five (0.4%), five (1.7%), and three patients (0.3%), respectively (**Fig. 1**). The incidence of IS was significantly higher in patients who underwent concomitant CAG and ITA than in those who underwent only diagnostic CAG (p = 0.014) or only PCI (p = 0.013). No statistically significant difference was observed in the incidence of IS between patients who underwent CAG alone and those who underwent PCI (p = 0.775). Regarding the access site, although there was no significant difference in the upper extremity approach between patients with and without IS (69.2% vs. 56.6%, p = 0.360), the brachial approach was significantly more frequent in patients with IS than in those without IS (23.1% vs. 5.7%, p = 0.007). There were no significant differences in the fluoroscopic time or contrast volume between the two groups. Regarding anticoagulation during the procedures, 2,000 units and 5,000 units of heparin were administered before CAG and during PCI, respectively. For CAG, an additional 2,000 units of heparin were administered one hour after the beginning of the procedure. During PCI, the dose of additional heparin was determined by measuring the activated coagulation time (ACT) to maintain a value >250 s.

Univariate and Multivariate Analysis for the Risk Factors of IS

The results of univariate and multivariate analysis for the risk factors of IS are shown in **Table 2**. Multivariate analysis revealed that age (odds ratio [OR], 1.117; 95% confidence interval [CI], 1.026-1.216; p = 0.011), AF (OR, 6.317; 95% CI, 1.578-25.280, p = 0.009), current smoking (OR, 40.694; 95% CI, 7.817-211.830; p < 0.001), prior CABG (OR, 6.272; 95% CI, 1.367-28.791; p = 0.018), prior stroke (OR, 17.997; 95% CI, 4.504-71.910; p < 0.001), additional ITA angiography (OR, 6.912; 95% CI, 1.847-25.867; p = 0.004) and the brachial approach (OR, 5.439; 95% CI, 1.201-24.629; p = 0.028) were independent risk factors for IS.

Location of IS

Six patients developed IS in the basilar artery (BA) or vertebral artery (VA) territory (posterior cerebral circulation), four patients developed IS in the middle cerebral artery (MCA) territory (anterior cerebral circulation), two patients developed IS in multiple areas, and one patient developed IS in an undetermined area (**Table 2**). Among the eight patients who presented with a sinus rhythm, IS was observed to have occurred in the BA or VA territory in five (62%), in the MCA territory in two (25%), and in multiple areas in one (13%). Among the five patients who presented with AF, IS was observed to have occurred in the BA or VA territory in one (20%), in the MCA territory in two (40%), in multiple areas in one (20%), and in undetermined areas in one patient (20%). IS developed in the territory of the posterior cerebral circulation in all five patients who underwent CAG concomitant with ITA angiography and in one patient who underwent PCI; IS was observed to have occurred in the other areas in the remaining seven patients (**Table 3**).

Neurological Course and Treatment of IS

The mean NIHSS score at the onset of IS was 6.9 ± 9.3 (one patient had 37 points, one had 11 points, and the others had < 10 points), which improved to 3.1 ± 8.2 at the time of discharge. Five patients showed complete remission at discharge (mRS = 0), seven showed residual neurological deficits (mRS = 2.7 ± 1.7, including two cases of severe deficit), and one died (mRS = 6). Heparin therapy was administered during the acute phase of IS in 10 patients, and tissue plasminogen activator (tPA) was administered to one patient who demonstrated the highest NIHSS score. In the 10 patients treated with heparin, the NIHSS score significantly improved (3.7 ± 2.9 to 0.7 ± 0.9, p = 0.004) (**Fig. 2**). The patient treated with tPA also

Table 2 Univariate and multivariate analysis of the risk factors for procedure-related ischemic stroke

	Univariate analysis			Multivariate analysis					
				Model 1			Model 2		
	Odds ratio	95% CI	p value	Odds ratio	95% CI	p value	Odds ratio	95% CI	p value
Age	1.073	1.007-1.144	0.030	1.115	1.026-1.212	0.011	1.117	1.026-1.216	0.011
Male	0.542	0.177-1.661	0.284	0.316	0.083-1.204	0.091	0.293	0.075-1.142	0.077
Atrial fibrillation	6.789	2.204-20.914	<0.001	6.723	1.705-26.508	0.006	6.317	1.578-25.280	0.009
Current smoking	9.808	3.009-31.970	<0.001	34.859	7.489-162.267	<0.001	40.694	7.817-211.830	<0.001
Prior MI	5.357	1.793-16.007	0.003	3.639	0.992-13.348	0.051	3.653	0.999-13.359	0.050
Prior CABG	4.062	1.109-14.879	0.034	6.272	1.367-28.791	0.018			
Prior stroke	12.068	4.016-36.270	<0.001	16.988	4.361-66.181	<0.001	17.997	4.504-71.910	<0.001
Cilostazol use	5.152	1.404-18.909	0.013	2.750	0.509-14.850	0.240	2.065	0.375-11.387	0.405
Additional ITA angiography	5.361	1.743-16.494	0.003				6.912	1.847-25.867	0.004
Brachial approach	4.652	1.268-17.062	0.020	3.833	0.865-16.975	0.077	5.439	1.201-24.629	0.028

CABG: coronary artery bypass grafting, CI: confidence interval, ITA: internal thoracic artery

Table 3 Relationship between the catheterization procedure and location of ischemic stroke

Type of procedure	Number of procedures performed	Number of IS (%)	Anterior Circulation (MCA territory)	Posterior circulation (BA or VA territory)	Multiple	Undetermined
Total	2,848	13 (0.46%)	4	6	2	1
sinus		8	2	5	1	0
AF		5	2	1	1	1
CAG	1,626	5 (0.31%)	4	0	0	1
PCI	921	3 (0.33%)	0	1	2	0
ITA	301	5 (1.66%)	0	5	0	0

AF: atrial fibrillation, BA: basilar artery, CAG: coronary angiography, IS: ischemic stroke, ITA: internal thoracic artery angiography, MCA: middle cerebral artery, PCI: percutaneous coronary intervention, VA: vertebral artery

showed an improvement in the NIHSS score. However, two patients did not respond to antithrombotic therapy, and their NIHSS scores deteriorated. These two patients presented with Stanford type A aortic dissection and heparin-induced thrombocytopenia.

Discussion

The main findings of this study are as follows. First, 0.46% of the patients who underwent cardiac catheterization developed symptomatic IS requiring treatment in the stroke care unit. Second, five unmodifiable factors (age, AF, current smoking, prior stroke, and prior CABG) and two modifiable risk factors (additional ITA angiography and the transbrachial approach) were identified as risk factors for IS following cardiac catheterization. Third, in patients receiving antithrombotic therapy for IS, a significant improvement in the neurological findings was observed. To our knowledge, this is the first study to investigate the neurological prognosis and efficacy of antithrombotic therapy for IS following cardiac catheterization using the NIHSS score and mRS.

Incidence of Ischemic Stroke after Cardiac Catheterization

In the present study, 0.46% of patients who underwent cardiac catheterization developed symptomatic IS requiring treatment in the stroke care unit. The incidence of IS was 0.4% after diagnostic CAG, 1.7% after CAG concomitant with ITA angiography, and 0.3% after PCI. In previous studies, the incidence of IS after cardiac catheterization was reportedly 0.11%-0.15%[1,5] and that after PCI ws 0.22%-0.38%[2-4]. Compared to these studies, the incidence of IS after diagnostic cardiac catheterization in our study population was marginally higher, although the incidence after PCI was within the reported range.

Unmodifiable and Modifiable Risk Factors for IS Following Cardiac Catheterization

In this study, we identified seven risk factors for IS following cardiac catheterization: age, current smoking, prior stroke, prior CABG, AF, additional ITA angiography, and the transbrachial approach. Among these, the

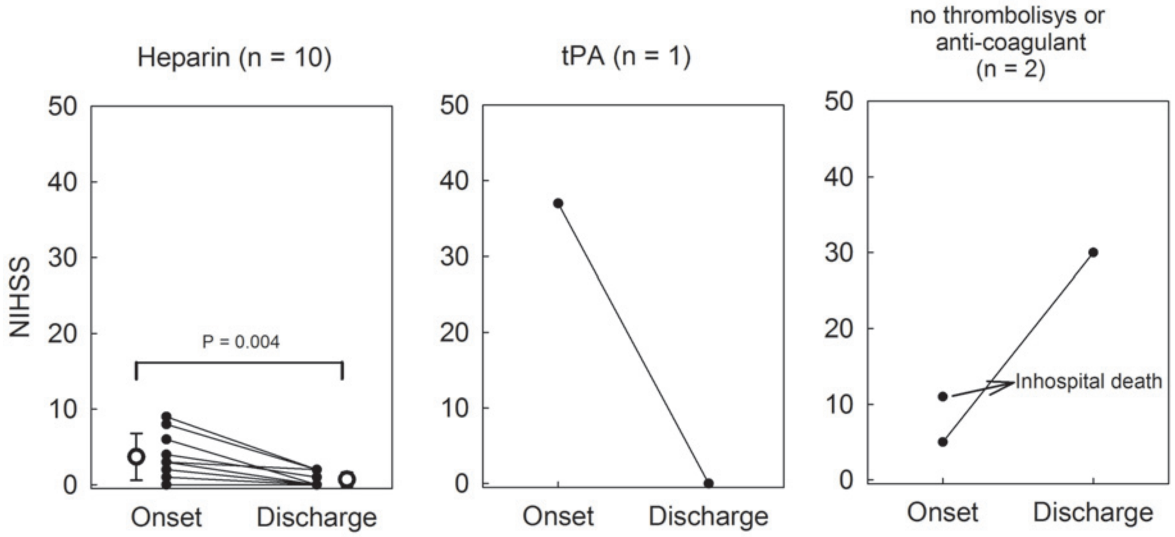

Fig. 2 Changes in the National Institutes of Health Stroke Scale (NIHSS) scores between the onset of ischemic stroke and time of discharge in patients who received anticoagulant therapy with heparin (n = 10), thrombolytic therapy with tissue plasminogen activator (tPA, n = 1) and neither anticoagulants nor thrombolytics (n = 2). The NIHSS score at the time of discharge could not be evaluated in one patient who received neither of them and died in hospital.

first four are closely related to the severity of atherosclerosis; patients presenting with these factors are considered high-risk patients who are more likely to have a greater number of fragile plaques and debris in the aorta that can become dislodged during catheter manipulation, resulting in embolic infarction. AF is a common risk factor for cerebral embolism irrespective of the catheterization procedure. These five factors are considered unmodifiable risk factors for IS following cardiac catheterization. In addition to these risk factors, modifiable risk factors that can be avoided or managed through clinical efforts have been reported, including the duration of fluoroscopy, amount of contrast medium used[5], and left ventricular angiography[5]. Kim et al.[13] reported that ITA angiography increases the risk of asymptomatic embolic cerebral infarction. They also demonstrated that the risk of silent cerebral infarction was > 10 times higher in patients who underwent screening using diffusion-weighted MRI after cardiac catheterization. Our findings are in agreement with those of Kim et al.[13], indicating that ITA angiography can be a significant risk factor for symptomatic IS requiring management in the stroke care unit.

Recently, CABG surgery has been performed using arterial bypass grafts because their patency is reportedly better than that of vein bypass grafts[14]. Therefore, additional ITA angiography should be performed in patients undergoing CABG with arterial bypass grafts. Because the ITAs originate from the bilateral subclavian arteries, the catheter must be advanced beyond the aortic arch. Since additional ITA angiography has been shown to be a modifiable risk factor for IS, noninvasive evaluation such as CT angiography should be considered before proceeding to invasive angiography in patients with prior CABG.

In this study, patients who underwent catheterization procedures using the brachial approach showed a significantly higher incidence of IS. The brachial approach requires manipulation of the guidewire closer to the cerebral arteries than is the case with other access sites. However, it is still unclear whether access sites influence the risk of IS[15–18]. Most previous studies compared the radial and femoral approaches because these two approaches are the major ones. Although the brachial approach was not often used in the cases we investigated for our study, we believe the radial or femoral approach may be preferable for avoiding IS, especially in high-risk patients.

Relationship between the Location of Ischemic Stroke and Catheterization Procedure

The primary mechanism of IS following cardiac catheterization can be explained as follows: intraprocedural catheter and wire manipulation dislodge pre-existing or newly developed thrombi or atherosclerotic debris from the aortic arch, proximal to the common carotid and VA[6,7]. In this study, we analyzed the relationship between procedural factors and the infarction site. Cerebral arteries are usually divided into the anterior and posterior cerebral circulation[9,19]. The former includes the internal carotid, MCA, and anterior cerebral arteries, while the latter includes the VA, BA, and posterior cerebral arteries. In our study, all five patients who developed IS after ITA angiography had IS of the posterior circulation. We hypothesized that this was because the ITA angiography procedure requires catheter and wire manipulation in the vicinity of the VAs, which are among the primary vessels supplying the posterior circulation because both the left VA and ITA originate from the left subclavian artery.

Clinical Outcomes after the Onset of Ischemic Stroke

In this study, we used the NIHSS and mRS tools to evaluate the clinical outcomes after the onset of IS. The NIHSS is a 15-item scale that provides quantitative assessment of the key components of a standard neurological examination[10,19]. This scale was designed for use in clinical trials to assess differences among the interventions required, although its use is increasing in patient care as an initial assessment tool and for planning post-acute care disposition[20,21]. Moreover, the clinical predictive validity of the NIHSS has been proven in several studies[20–23]. The mRS measures functional independence on a 7-grade scale[11]. It has been used as a measure of stroke-related handicaps in many interventional trials and is frequently used as a global measure of the functional impact of stroke[24,25].

Among the 13 patients who developed IS, seven showed a residual neurological deficit, including two with a severe deficit (mRS = 5) and one who died (mRS = 6). Thus, the mortality rate after IS was 7.7%, and 14.4% of the patients showed severe residual damage. Mortality rates of between 11 and 48% have been reported in previous studies[1–3,5], along with an incidence of moderate-to-severe residual neurological disorders of 31%[3]. One of the two patients in our study who demonstrated severe deficits had had multiple infarctions, as had the one patient who died. In contrast, patients with localized infarctions developed only mild or moderate deficits. We attribute this to the difference in initial infarct volume, because multiple infarctions are known to cause larger areas of infarction. Another study demonstrated that the initial infarct volume was an independent predictor of stroke outcome, as evaluated using the mRS and NIHSS 90 days post infarction[26].

Most patients were administered anticoagulants or thrombolytic therapy for the management of IS after cardiac catheterization. These treatment modalities could not be administered to the two patients who presented with a Stanford type A aortic dissection or heparin-induced thrombocytopenia and showed poor neurological prognosis. Treatment of IS with anticoagulants or thrombolytics is important after cardiac catheterization and should be emphasized in clinical practice.

Study Limitations

First, this was a retrospective analysis performed at a single institution, so selection bias is possible. Second, because we focused exclusively on patients with clinically significant IS requiring intensive treatment in a stroke care unit, the number of patients with IS was small and we could not assess the risk of silent or minor IS after cardiac catheterization. And third, the data we used were relatively old, but we chose to investigate patients undergoing cardiac catheterization between January 2011 and December 2013 because detailed neurological assessment was performed at the onset of IS and time of discharge during that period. Recently, endovascular treatment (EVT) has been recommended for acute ischemic stroke[27]. None of the patients underwent EVT in the present study because EVT for IS was not standard during the study period. A large-scale prospective study is required to confirm our findings.

Conclusion

Although rare, IS after cardiac catheterization is associated with significant morbidity and mortality. Avoiding unnecessary ITA angiography and the brachial approach may help in reducing the incidence, and appropriate treatment using anticoagulants or thrombolytics may improve prognosis and reduce residual neurological deficits.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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