



Prospective Study on the Incidence of Cerebrovascular Disease After Coronary Angiography

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Aim: Previous studies have reported a 10.2%–22% rate of silent cerebral infarction and a 0.1%–1% rate of symptomatic cerebral infarction after coronary angiography (CAG). However, the risk factors of cerebral infarction after CAG have not been fully elucidated. For this reason, we investigated the incidence and risk factors of CVD complications within 48 h after CAG using magnetic resonance imaging (MRI) (Diffusion-weighted MRI) at Kagoshima University Hospital.

Methods: From September 2013 to April 2015, we examined the incidence and risk factors, including procedural data and patients characteristics, of cerebrovascular disease after CAG in consecutive 61 patients who underwent CAG and MRI in our hospital.

Results: Silent cerebral infarction after CAG was observed in 6 cases (9.8%), and they should not show any neurological symptoms of cerebral infarction. Only prior coronary artery bypass grafting (CABG) was more frequently found in the stroke group ($n=6$) than that in the non-stroke group ($n=55$); however, no significant difference was observed ($P=0.07$). After adjusting for confounders, prior CABG was a significant independent risk factor for the incidence of stroke after CAG (odds ratio: 11.7, 95% confidence interval: 1.14–129.8, $P=0.04$).

Conclusions: We suggested that the incidence of cerebral infarction after CAG was not related to the catheterization procedure per se but may be caused by atherosclerosis with CABG.

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Key words: Cerebral infarction, Coronary angiography, Magnetic resonance imaging

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Introduction

The magnitude of cerebrovascular disease (CVD) related to coronary catheterization is high and sometimes severe. It is considered one of the most severe complications after coronary angiography (CAG). We have observed the occurrence of CVD complications after percutaneous coronary intervention (PCI) as well as after the only examination technique such as CAG.

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Although the frequency of symptomatic CVD complications was explained to patients filling the catheter examination consent form at our facility, the frequency of asymptomatic CVD complications was not explained completely in the real clinical practice because it has not been substantially investigated.

Previous studies have reported the rate of symptomatic CVD complications after CAG and PCI to be 0.1%–1%¹⁻³⁾ and 0.1%–0.6%⁴⁻⁹⁾, respectively. However, the rate of asymptomatic CVD is 10.2%–22%, which is significantly higher than that of symptomatic CVD¹⁰⁻¹³⁾. In addition, there are multiple risk factors of CVD after PCI and CAG including advanced age, hypertension, diabetes mellitus (DM), prior stroke, and the use of intra-aortic balloon pumping (IABP)^{9, 13-16)}. It has been shown that CVD after CAG or PCI is

associated with a poor prognosis^{9, 14-16}. Recently, cardiac catheterization has shifted from the femoral artery to the radial artery approach, and slender catheters such as 4 Fr or 5 Fr catheters are commonly used. In addition, because of the aging Japanese population, CAG and PCI are being performed even in those aged ≥ 75 years. Because few studies have reported on the relationship between CVD complications after CAG or PCI and the procedural data such as puncture site, dosage of contrast medium, procedure time, catheter size, CVD complication risks remains unknown in Japan. Therefore, we investigated the incidence and risk factors of CVD complication within 48 h after CAG using diffusion-weighted magnetic resonance imaging (DW-MRI) at our institute.

Methods

Subjects and Study Protocol

We conducted a prospective study including patients who underwent CAG and were admitted to Kagoshima University Hospital between September 2013 and April 2015. In the patients who underwent several CAG, the first CAG was used in this study. Patients who corresponded to MRI exclusion criteria and were considered inappropriate by the physician were excluded from the study. The patients underwent MRI of their heads within 48 h after CAG, with or without symptoms, and MRI interpretation was performed immediately by a radiologist in a blinded manner.

All patients gave their written informed consent prior to participating in the study and were the subjects of this analysis. This study complied with the standards of the Declaration of Helsinki and current ethical guidelines, and it was approved by the institutional ethics board at Kagoshima University Hospital. Maximum effort was taken by all involved in this study to ensure anonymity and protection of subject information. We referred to the case identification cord instead of the medical record number of each subject.

Coronary Angiography

CAG was performed by well-trained cardiologists according to the standardized Judkins method. All patients underwent CAG using 4 to 6 Fr catheters via femoral or radial access, as selected based on the operator's judgment. In addition, we did not perform the left ventricle (LV) graphy routinely in the patients with aortic stenosis because there is a possibility of high rate of CVD complications. Before starting the procedure, patients were administered 3000 U of unfractionated heparin intravenously. A non-ionic iso-osmolar contrast medium was used during CAG. The total fluoroscopy time was measured in all cases.

Measurements

Blood specimens for the measurement of BNP and lipoprotein (a) levels were collected at the time of admission. A blood sample for the measurement of Cystatin C was collected before CAG.

Hypertension was defined as having systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or by the use of antihypertensive drugs. DM was defined as having an HbA1c level of $\geq 6.5\%$, or occasionally, a blood glucose level of ≥ 200 mg/dL, fasting blood glucose level of ≥ 126 mg/dl, or a history of treatment for diabetes. Dyslipidemia was defined as having a low-density lipoprotein cholesterol level of ≥ 140 mg/dL, triglyceride level of ≥ 150 mg/dL, high-density lipoprotein cholesterol level of ≤ 40 mg/dL, or the use of lipid-lowering drugs such as statin and fibrates. CAD was defined as a diameter stenosis of the presence of ≥ 1 vessel with $\geq 70\%$ luminal diameter narrowing, as detected by CAG during the present study or previous CAG by the American College of Cardiology/American Heart Association for lesion classification in three coronary arteries¹⁷. Prior heart failure was defined as having a principal discharge diagnosis of heart failure. Aortic stenosis was defined as mild or over, and aortic regurgitation was defined as trace or over, according to the guidelines¹⁸.

MRI

DW-MRI of the brain [1.5- or 3-Tesla (T) Achieva Nova Dual, Philips Medical Systems, Netherlands] was performed within 48 h after CAG. The imaging protocol included DW single-shot spin echo-planar imaging [repetition time (TR): 4500 ms (1.5-T), 4000 ms (3-T); echo time (TE): 74 ms (1.5-T), 87 ms (3-T); slice thickness: 5 mm (1.5-T and 3-T); interslice gap: 1 mm (1.5-T and 3-T); 24 axial slices (1.5-T and 3-T); matrix: 102×128 (1.5-T and 3-T); field view: 220 mm (1.5-T and 3-T); diffusion gradient: b values of 0 and 1000 s/mm^2 (1.5-T and 3-T, respectively)], fluid-attenuated inversion recovery [TR/TE/inversion time (TI): 9000/119/2500 ms (1.5-T), 9000/123/2500 ms (3-T)], and T2-weighted turbo spin echo [TR/TE: 4000/89 (1.5-T), 4000/87 ms (3-T)] sequences. All MRI findings were analyzed by 2 radiologists in a blinded manner. We diagnosed acute embolic infarction using the combination of DW and apparent diffusion coefficient (ADC) map findings.

Statistical Analysis

Descriptive statistics are presented as frequency (percentage) for categorical variables and mean \pm standard deviation or median (interquartile range) for continuous variables. The data were compared using a chi-square or Fisher's exact test for a categorical vari-

Table 1. Baseline Characteristics of Patients with (CVD) and without (non-CVD) Stroke after CAG

Variables	All patients N=61	CVD N=6	non-CVD N=55	P value
(A) Clinical characteristics				
Age (years)	70.0 ± 10.2	65.5 ± 4.2	70.5 ± 1.4	0.3
Age ≥ 75 years	23 (38%)	1 (17%)	22 (40%)	0.4
Male	43 (70%)	3 (50%)	40 (73%)	0.3
BMI	23.9 ± 4.0	23.8 ± 1.6	23.9 ± 0.5	0.97
BMI < 25.0	36 (59%)	3 (50%)	33 (60%)	0.7
Hypertension	44 (72%)	3 (50%)	41 (75%)	0.3
Diabetes mellitus	25 (41%)	1 (17%)	24 (44%)	0.4
Dyslipidemia	41 (67%)	5 (83%)	36 (65%)	0.7
Current smoking	11 (18%)	1 (17%)	10 (18%)	1.0
Prior Heart failure	8 (13%)	1 (17%)	7 (13%)	1.0
Coronary artery disease	43 (70%)	4 (67%)	39 (71%)	1.0
Multi-vessel disease	19 (31%)	3 (50%)	16 (29%)	0.4
Aortic stenosis	7 (11%)	1 (17%)	6 (11%)	0.5
Aortic regurgitation	22 (36%)	3 (50%)	19 (35%)	0.7
Mitral regurgitation grade $\frac{3}{4}$	8 (13%)	1 (17%)	7 (13%)	1.0
Ejection fraction	61.4 (48.5–69)	58.5 (50.5–68.3)	62 (47.9–74.5)	0.7
Ejection fraction < 40%	6 (9.8%)	1 (17%)	5 (9.1%)	0.5
Prior PCI	28 (46%)	2 (33%)	26 (47%)	0.7
Prior CABG	5 (8.2%)	2 (33%)	3 (5.5%)	0.07
Prior myocardial infarction	14 (23%)	1 (17%)	13 (24%)	1.0
Prior Stroke	6 (9.8%)	0 (0%)	6 (11%)	1.0
Aortic aneurysm/dissection	9 (1.8%)	1 (17%)	8 (15%)	1.0
Peripheral vascular disease	9 (1.8%)	1 (17%)	8 (15%)	1.0
eGFR < 60, not on dialysis	18 (30%)	1 (17%)	17 (31%)	0.7
Dialysis	2 (3.2%)	1 (17%)	1 (1.8%)	0.2
Atrial fibrillation	5 (8.2%)	0 (0%)	5 (9.1%)	1.0
Anemia (Hb < 11.0g/dL)	10 (16%)	1 (17%)	9 (16%)	1.0
Platelets < 100 × 10 ⁹ /L	1 (1.6%)	0 (0.0%)	1 (1.8%)	1.0
COPD	5 (8.2%)	0 (0.0%)	5 (9.1%)	1.0
Liver hepatitis	2 (3.2%)	0 (0.0%)	2 (3.6%)	1.0
Malignancy	7 (11%)	0 (0%)	7 (13%)	1.0
mean PWV	1785 ± 463	1994 ± 973	1762 ± 378	0.6
mean CAVI	8.8 ± 1.6	8.0 ± 1.2	8.9 ± 1.6	0.2
BNP	52.6 (26.4–111.6)	56.5 (41.6–712.6)	52.6 (26–109.4)	0.5
Lp (a)	15.4 (6.5–32.5)	14.4 (5.6–29.6)	15.4 (6.5–33)	0.8
Cystatin C	1.08 (0.93–1.3)	1.09 (0.82–2.7)	1.08 (0.93–1.3)	0.9
(B) Baseline Medications				
Antiplatelet therapy				
Thienopyridine	36 (59%)	3 (8.3%)	33 (92%)	0.7
Ticlopidine	7 (11%)	0 (0%)	7 (13%)	1.0
Clopidogrel	29 (48%)	3 (50%)	26 (47%)	1.0
Aspirin	46 (75%)	5 (83%)	41 (75%)	1.0
Cilostazol	1 (1.6%)	0 (0%)	1 (1.8%)	1.0

(Cont Table 1)

Variables	All patients N=61	CVD N=6	non-CVD N=55	P value
(B) Baseline Medications				
Other medications				
Statins	40 (66%)	4 (67%)	36 (65%)	1.0
Beta-blockers	22 (36%)	1 (17%)	21 (38%)	0.4
ACE-I/ARB	37 (61%)	3 (50%)	34 (62%)	0.7
Nitrates	7 (11%)	1 (17%)	6 (11%)	0.5
Calcium channel blockers	31 (51%)	1 (17%)	30 (55%)	0.1
Nicorandil	30 (49%)	2 (33%)	28 (51%)	0.7
Warfarin	7 (11%)	1 (17%)	6 (11%)	0.4
DOAC	1 (1.6%)	0 (0%)	1 (1.8%)	1.0

Continuous variables are shown as mean \pm SD or median (interquartile range).

ACE-I=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker, BMI=body mass index, BNP=brain natriuretic peptide, CABG=coronary artery bypass grafting, CAVI=cardio ankle vascular index, COPD=chronic obstructive pulmonary disease, CVD=cerebrovascular disease, DOAC=direct oral anticoagulants, eGFR=estimated glomerular filtration rate, Hb=hemoglobin, Lp (a)=lipoprotein (a), LV=left ventricle, PCI=percutaneous coronary intervention, and PWV=pulse wave velocity.

able, a two-sample *t*-test for normal distribution, or the Wilcoxon rank sum test for non-normal distribution of continuous variables. 95% confidence interval (CI) of binominal proportions was calculated using the adjusted Wald method¹⁹. A multiple logistic regression model was used to assess CVD risk factor complications that were expressed as odds ratios with a 95% CI, and adjusted by which a dummy variable was the advanced age assigned 75 years old and more as 1. All analyses were conducted using JMP 12.0 (SAS Institute Inc, Cary, NC). All statistical analyses were two-tailed, and *P* value <0.05 was considered statistically significant.

Results

Baseline Characteristics

The baseline characteristics of the patients are shown in **Table 1**. The mean age was 70.0 ± 10.2 years, and 43 (70%) patients were male. Of the 61 patients, 25 (41%) presented with DM, 41 (67%) with dyslipidemia, 44 (72%) with hypertension, and 5 (8.2%) with atrial fibrillation. 28 (46%) patients underwent PCI and 5 (8.2%) underwent CABG. In addition, 14 (23%) patients had prior myocardial infarction. In terms of procedural characteristics, a catheter size of <5 Fr was frequently used (67%), mean procedural time was 66.5 ± 19.9 min, and 10 (16%) patients underwent CAG via the femoral artery. Ergonovine provocation test was performed in 9 patients (15%), angiography of the internal mammary arteries (IMA) was performed in 1 patient (1.6%), and angiography of

the saphenous vein was not done at all. Additionally, LV graphy was performed in 4 (6.6%) patients (**Table 2**). Regarding baseline medications, no significant difference was observed in the use of antiplatelet drugs, statins, beta-blockers, warfarin, or direct oral anticoagulants (DOAC).

The Incidence and Location of CVD Complications

The incidence of asymptomatic cerebral infarction (CI) complication after CAG was 9.8% (6 cases), with a mid-point percentage 11.1% (95% Confidence Interval: 4.3%–20.2%) calculated using the adjusted Wald method. Symptomatic cerebral infarction or symptomatic and asymptomatic cerebral hemorrhage was not observed. There were 2 cases (case 1 and 6) with an infarct lesion size > 3 mm. **Table 3** shows the location of stroke and procedural data of CAG in each patient with asymptomatic stroke after CAG. **Fig. 1** shows MRI images of each patient with stroke after CAG. Only case 3 developed a cerebral infarct at two sites, whereas other cases presented with a cerebral infarct at only one site. Only one case underwent CAG via the right femoral approach, whereas the approach site of other cases was via the right radial artery. No cases underwent any IMA angiography and IABP, which were reported as risk factors of CVD after CAG or PCI.

Baseline Characteristics: CVD Group vs. Non-CVD Group

We compared the baseline characteristics of patients

Table 2. Procedural Characteristics of Patients with (CVD) and without (non-CVD) Stroke after CAG

Variables	All patients N=61	CVD N=6	non-CVD N=55	P value
Dose of Heparin >3000 U	2 (3.3%)	0 (0%)	2 (3.6%)	1.0
Procedural time (min)	66.5 ± 19.9	61.3 ± 12.9	67.1 ± 20.5	0.5
Dosage of contrast medium	68.8 ± 34.8	55.8 ± 26.2	70.3 ± 35.4	0.3
Femoral artery catheterization	10 (16%)	1 (17%)	9 (16%)	1.0
EM provocation	9 (15%)	1 (17%)	8 (15%)	1.0
SVG angiography	0 (0%)	0 (0%)	0 (0%)	–
IMA angiography	1 (1.6%)	0 (0%)	1 (1.8%)	1.0
LV graphy	4 (6.6%)	0 (0%)	4 (7.3%)	1.0

CAG = coronary angiography, EM = ergonovine malate, IMA = internal mammary artery, LV = left ventricle, and SVG = saphenous vein graft.

Table 3. Location of Stroke and Procedural Data from each patient with Stroke after CAG

Case No.	Location of stroke	Diagnosis after CAG	Age	Sex	Ergonovine test	Catheter size (Fr)	Heparin (U)	Procedural time (min)	Contrast medium (mL)	Access site
1	left corona radiata	Vasospastic angina	68	F	present	5	3000	75	60	right radial
2	splenium of corpus callosum	Silent myocardial ischemia	61	M	absent	6	3000	73	60	right radial
3	right thalamus and right parietal lobe	Unstable angina	65	M	present	4	3000	50	100	right radial
4	right cerebellar hemisphere	Aortic regurgitation	52	F	absent	5	3000	55	50	right femoral
5	right frontal lobe	Abdominal aortic aneurysm	65	M	absent	4	3000	70	20	right radial
6	left cerebellar hemisphere	Silent myocardial ischemia	82	F	absent	4	3000	45	45	right radial

CAG = coronary angiography, IMA = internal mammary artery, and SVG = saphenous vein graft.

with (CVD group, $n=6$) and without (non-CVD group, $n=55$) CVD complications.

Age, sex, DM, dyslipidemia, hypertension, multi-vessel disease, aortic stenosis, ejection fraction, prior myocardial infarction, and atrial fibrillation were similar between CVD and non-CVD groups. In addition, regarding procedural data, there was no significant difference in catheter size, heparin dosage, procedural time, access site, and LV graphy between both groups.

In terms of medication, no significant difference was observed in the use of antiplatelet drugs, warfarin, and DOAC. Prior CABG was more frequently found in the CVD group (2/6 cases, 33%) than that in the non-CVD group (3/55 cases, 5.5%); however, no significant difference was observed ($P=0.07$).

Independent Risk Factors for CVD Complications

We performed a multiple logistic regression analy-

sis after adjusting for age, sex, and prior CABG to identify the independent risk factors for CVD complications after CAG, because age and sex are the important meaningful factor in the clinical practice and only prior CABG was tended to be more frequently in the CVD group than in the non-CVD group. Our results demonstrated that prior CABG was a significant independent risk factor for the incidence of stroke after CAG (OR: 11.7, 95%CI: 1.14–129.8, $P=0.04$) (Table 4).

Discussion

The incidence of asymptomatic CI complications after CAG was 9.8% (6 cases); however, symptomatic or asymptomatic cerebral hemorrhage was not observed. In addition, prior CABG was a significant independent risk factor for the incidence of stroke after CAG, after adjusting for age and sex.

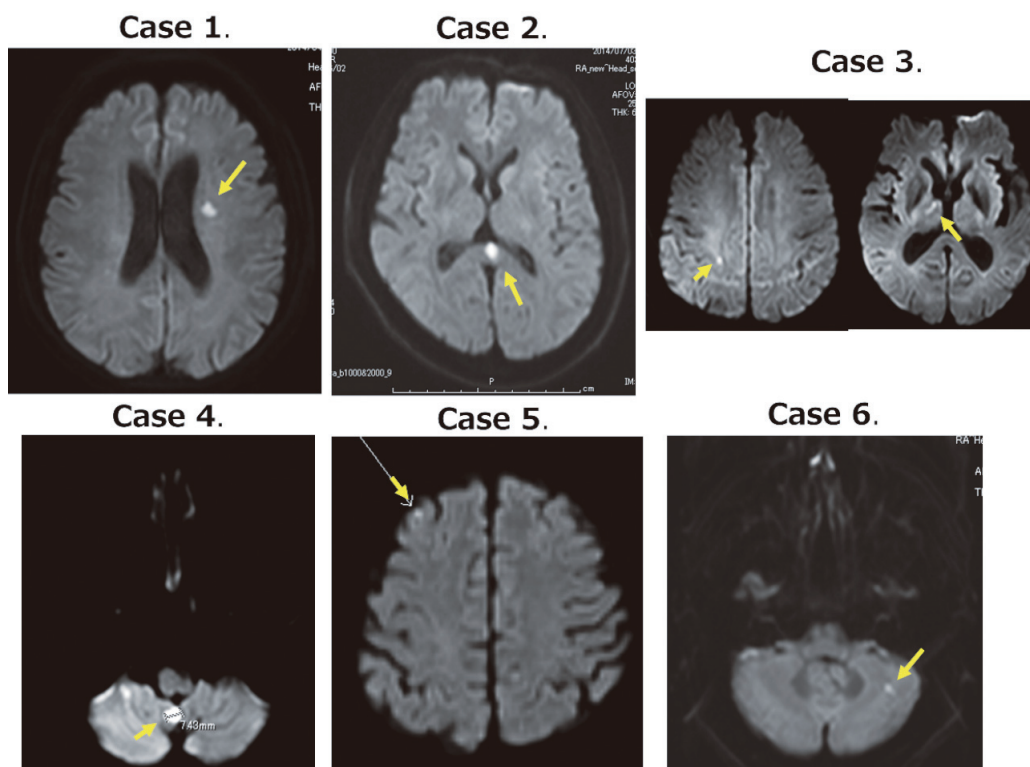


Fig. 1. DW-MRI images in each patient with stroke after CAG.

A yellow arrow shows acute embolic lesion which was characterized by a bright hyperintense lesion on DW and ADC maps.

Previous studies have reported a 10.2%–22% incidence of asymptomatic CI after CAG^{11, 13, 20}. Omran *et al.* reported a significantly high incidence rate (22%) of CI after retrograde catheterization of the aortic valve¹¹. Recently, Morita *et al.* reported that of the 84 patients who underwent MRI after catheterization, acute CI was found in 27 (32.1%) patients and the rate of CI after catheterization was significantly higher than other studies. However, because this study was a retrospective analysis and MRI was not performed for the series of catheterization procedures, the rate of CI may have been considerably overestimated²¹. In Korea, the incidence of asymptomatic CI after CAG performed before CABG and detected by MRI was 10.2% (20/197 patients), with IMA angiography as the independent risk factor¹³. We speculated that the incidence of stroke after PCI increased slightly compared with that after CAG because of the increase in time and complexity of the procedure. In an analysis of 9662 patients who underwent PCI, the incidence of symptomatic stroke after the procedure was 0.38% and the risk factors included the use of IABP, advanced age (>80 years), and vein graft intervention¹⁵. A prospective study in Germany reported that 7 (15%) of 48 patients exhibited 9 focal CI after cardiac catheterization, with

duration of the procedure as an independent predictor of CI occurrence¹⁰. IMA angiography is commonly performed both before and after CABG to confirm the presence and location. Similarly, vein graft angiography is usually performed after CABG. Therefore, patients who underwent IMA angiography and vein graft angiography either before or after CABG may have severe arteriosclerosis with multiple coronary stenosis. The performance of IMA angiography and vein graft after CABG decreased because the presence and location of IMA and vein graft were confirmed by CT-angiography instead of catheterization. Because the performance of IMA and saphenous vein graft (SVG) angiography was very low in this study, a significant difference between CVD and non-CVD groups was not observed. Therefore, we speculate that it is reasonable to consider prior CABG as a significant independent risk factor for the incidence of CI after CAG.

The complications of postprocedural CVD in CAG and PCI have been reported to be caused by thrombus formation in the catheter itself and lumen, attachment of the thrombus to the exchange wire, air embolisms, and debris from arteriosclerosis dislodged by guide catheter²²⁻²⁴. In accordance with previous

Table 4. A multiple logistic regression model to identify the independent risk factors for CVD after CAG

Variables	Present N of events/ N of patients	Absent N of events/ N of patients	Univariate		Multivariate	
			OR (95%CI)	<i>P</i> value	OR (95%CI)	<i>P</i> value
Prior CABG	2/5 (40%)	4/56 (7.1%)	8.67 (0.94-70.5)	0.06	11.7 (1.14-129.8)	0.04
Age ≥75 years	1/23 (4.4%)	5/38 (13%)	0.30 (0.02-2.03)	0.2	0.24 (0.01-2.14)	0.2
Male	3/43 (7.0%)	3/18 (17%)	0.38 (0.06-2.22)	0.3	0.22 (0.02-1.55)	0.1

CABG = coronary artery bypass grafting, CAG = coronary angiography, CI = confidence interval, CVD = cerebrovascular disease, OR = odds ratio

studies, we found that asymptomatic CI was observed in 9.8% of the patients in our study. Even with the recent use of a small diameter catheter such as the 4 Fr catheter, the incidence of CI did not differ compared with that when a larger size catheter was used. In addition, we demonstrated that all procedural data including heparin dosage, procedural time, and dosage of contrast medium were not risk factors of CVD. The procedures were performed only by skilled operators, so that no unsuccessful cases were reported. This study included cases with only CAG, and without PCI, which minimized catheter-related complications. In a 2012 report from Europe, 165 patients with advanced aortic valve stenosis were assigned to either the femoral artery approach or the radial artery approach, and 77 patients from the femoral artery group and 83 patients from the radial artery group were analyzed. Asymptomatic CI detected by DW-MRI was not significantly different between the femoral artery and radial artery groups (11.7% vs 17.5%, respectively, $P=0.31$). The independent risk factors were high height and low aortic pressure gradient²⁵. Considering that the catheter in the radial artery group did not pass through the aortic arch, it was likely that the incidence of CI in this group was lesser than that in the femoral artery group; however, no significant difference was reported between two groups. We speculated that the postprocedural CVD complications in the recently developed catheterization procedure was not affected significantly by the procedure itself, which did not contribute as a risk factor of CVD.

In previous studies, the in-hospital mortality rate after symptomatic CVD complications during catheter examination and treatment has been reported to be 22%–37%, which is a very poor prognosis^{9, 14, 15, 26, 27}. Although spontaneous asymptomatic CI increases with age, it has been reported to be 8%–28% across all generations²⁸. In patients with cardiovascular disease, the incidence of asymptomatic CI is known to be extremely high^{29, 30}. Recent report demonstrated that the incidence rate of non-fatal stroke for 3-years after PCI in the drug-eluting stent era in patients with renal

insufficiency was 3.8%³¹. Furthermore, silent brain infarction is associated with a 2-fold increased risk of future stroke³².

Study Limitations

There are several limitations in this study. First, the present study is an observational study; therefore, unknown risk factors may exist. However, we extracted detailed data as much as possible. Secondly, 61 cases from a single facility is a small sample size and statistically insufficient to investigate the risk factors of CVD. Further studies with large sample sizes are required. Finally, because the procedures, particularly the access site of the catheter, were not allocated in this study, we could not clarify the difference among the procedures.

Conclusions

The incidence of the asymptomatic CI detected by MRI after CAG was 9.8%, but no onset of symptomatic CI was observed. Only prior CABG was found to be an independent risk factor for the development of asymptomatic CI. We suggest that the incidence of CI after CAG was not related to the catheterization procedure per se but caused by severe atherosclerosis and multiple coronary stenosis in patients who underwent CABG.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

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