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ORIGINAL ARTICLE

Postoperative neurological complications and risk factors for pre-existing silent brain infarction in elderly patients undergoing coronary artery bypass grafting

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Abstract
Purpose Elderly patients with multiple infarctions revealed a high prevalence of postoperative stroke after coronary artery bypass grafting (CABG). However, postoperative neurological complications and characteristics of silent brain infarction (SBI) have not been evaluated in elderly patients undergoing CABG.
Methods Four hundred forty-nine patients (≥60 years old) scheduled for CABG underwent cerebral magnetic resonance imaging (MRI) and MR angiography preoperatively to assess cerebral infarctions and carotid and intracranial artery stenosis. Atherosclerosis of the ascending aorta was assessed by epiaortic ultrasound during surgery. Patients were sorted by their history of cerebrovascular disease (CVD) and the presence of infarction by MRI: SBI (infarction without CVD), BI (symptomatic brain infarction; CVD and infarction), and controls (no findings of either CVD or infarction).
Results SBI was found in 35.5% of the 449 patients and increased with age. The prevalence of pre-existing multiple infarctions was less frequent in SBI than in BI. The incidence of postoperative stroke and cognitive dysfunction was 1.3% and 4.9% in controls ($n = 225$), 5.7% and 15.2% in SBI ($n = 158$), and 9.1% and 18.2% in BI ($n = 66$). Patients with SBI were older and had more renal dysfunction and preoperative cognitive impairment. Stepwise logistic regression demonstrated that age, renal dysfunction, preoperative cognitive impairment, atherosclerosis of the ascending aorta, and intracranial arterial stenosis were associated significantly with SBI.
Conclusion Patients with SBI were ranked at moderate risk of neurological complications after CABG between control and BI. Increased age, renal dysfunction, and preoperative cognitive impairment appeared to be strongly associated with SBI.

Keywords Silent brain infarction · Atherosclerosis · Coronary artery bypass grafting

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Introduction

Adverse cerebral complications after CABG, including postoperative stroke and postoperative cognitive dysfunction (POCD), are associated with prolonged hospitalization, excessive operative mortality, high hospital costs, and altered quality of life. The etiology of postoperative stroke after CABG is multifactorial, and preoperative atherosclerotic risk factors, such as advanced age and atherosclerosis of the ascending aorta are risk factors for stroke after CABG [1–3]. A history of prior stroke has been also reported to be a risk factor for neurological complication after CABG [4]. Our previous study found that patients with preoperative multiple infarctions detected by magnetic resonance imaging (MRI) showed a significantly high incidence of stroke after CABG [5]. However, it was not evaluated whether patients with silent brain infarction (SBI) are at high risk of neurological complications after CABG. Moreover, it is not clear whether there are differences in the frequency of neurological complications after CABG among patients with SBI, with symptomatic brain

infarction (BI), and those without infarctions. Cerebral infarctions without neurological symptoms can be identified by cerebral imaging, such as MRI, but not all patients might be assessed by MRI before CABG. Determining the presence and risk factors of SBI might reduce the incidence of neurological complications after CABG.

SBI is common in healthy elderly people and describes a focal ischemic lesion detected by brain imaging without a history of transient ischemic attack (TIA) or stroke to explain the imaging findings [6]. Many studies have identified risk factors, including advanced age and hypertension [6], as associated with atherosclerosis. Although risk factors for SBI have been demonstrated in a population-based study, little is known about which atherosclerotic factors are associated with SBI in elderly patients who undergo CABG. The aim of this study was to compare the prevalence of neurological complications after CABG among patients with SBI, those with BI, and those without infarction and to evaluate risk factors for SBI in elderly patients who undergo CABG.

Methods

Study population

Our analysis was performed on data gathered prospectively from 463 patients aged 60 years and older who underwent elective CABG with cardiopulmonary bypass (CPB) by a single surgeon at Kumamoto Chuo Hospital. Demographic data and preoperative risk factors evaluated in this study included age, gender, hypertension, diabetes mellitus, hyperlipidemia, renal dysfunction (serum creatinine $\geq$1.9 mg/dl), peripheral vascular disease (PVD), abdominal aortic aneurysm (AAA), smoking, and history of cerebrovascular disease (CVD). CVD included stroke or TIA. Stroke was defined as an episode of typical focal neurological deficit lasting $\geq$24 h. TIA was defined similarly, but with symptoms lasting <24 h. The hospital institutional review board approved the study, and all patients provided written, informed consent to participate.

Patient management

Premedication was intramuscular morphine hydrochloride (5–10 mg) and scopolamine (0.3 mg). Anesthesia was induced with diazepam (5 mg), fentanyl (10 μg/kg), and vecuronium and maintained with fentanyl (total dose, 30 μg/kg, including the induction dose), diazepam, and isoflurane. CABG was performed under CPB with a roller pump, membrane oxygenators, and a 40-μm arterial blood filter, as described previously [5]. Moderate hypothermia (28°–34°C) and α-stat control of acid–base management was used. We maintained mean arterial pressure between 50 and 70 mmHg in patients without multiple infarctions and severe carotid stenosis during CPB. Mean arterial pressure was kept above 70 mmHg in patients with multiple brain infarctions or severe carotid stenosis.

Cerebrovascular and neurological evaluation

All patients underwent brain MRI to evaluate cerebral infarctions and MR angiography (MRA) to assess intracranial artery stenosis and carotid artery stenosis before surgery. Cerebral infarction was defined as a focal area that was visible as a low-intensity area on the T_1-weighted image and a high-intensity area on the T_2-weighted image. Ischemic changes or infarction in the brain on MRI were classified as almost normal, leukoaraiosis, some small infarctions with diameter <15 mm, and multiple small infarctions or broad infarctions. The locations of infarctions were classified as cerebral cortex, subcortical white matter, basal ganglia, cerebellum, and brainstem [7]. The degree of stenosis in the intracranial arteries was graded bilaterally by MRA as normal, mild (narrowing <50%), moderate (>50%), and severe (occluded). The degree of stenosis in the carotid artery was graded by MRA as normal, mild (narrowing <50%), moderate (50–75%), and severe (>75% or obstructed). Lesions on MRI and MRA were evaluated independently by two radiologists who were blinded to preoperative risk factors and symptoms.

Neurocognitive status was assessed before surgery using the Hasegawa Dementia Scale (HDS) in all patients. HDS is a modification of the Mini-Mental State Examination (MMSE), with a 30-point scale that measures cognitive function, including orientation, short-term memory, verbal recall, and attention. Preoperative cognitive impairment was defined as a point score less than 24 on the HDS (equivalent to 24 on the Mini-Mental State Examination). POCD was defined as a deterioration of 4 points (equal to 2 standard deviations from baseline) compared with the preoperative HDS. Patients with new global or focal neurological deficits lasting more than 24 h underwent postoperative MRI or computed tomography (CT) of the brain. Stroke was defined as new postoperative neurological deficits that were confirmed by postoperative brain MRI and CT and further verified by neurologists.

Evaluation of the ascending aorta

We evaluated atherosclerotic lesions of the ascending aorta by echocardiography using an epiaortic probe before cannulation. The degree of atherosclerosis in the ascending aorta was graded according to Wareing's method [8]: normal, mild (<3 mm intimal thickening), moderate

(≥3 mm intimal thickening involving one segment of the ascending aorta), and severe (≥3 mm intimal thickening involving two or all three segments, often with protrusions, ulcer of the surface, or mobile components).

Statistical analysis

For analysis, patients were divided into three groups according to their history of CVD and the presence of infarctions on brain MRI. The SBI group included patients who had infarctions without prior CVD. Patients in the BI group had both infarctions and a prior history of CVD. The control group had neither infarcts nor prior CVD. We excluded 14 patients with a prior history of CVD but no infarctions at present, leaving 449 patients eligible for analysis. One-way analysis of variance was used to compare data for age, aortic clamp time, and CPB time between groups. When appropriate, secondary tests were performed using the multiple comparisons. The chi-square test with Bonferroni correction for multiple comparisons was used to compare all nonparametric data between groups. For the comparisons of numbers and locations of infarctions between SBI and BI, statistical analysis was performed using the chi-square test. A P value less than 0.05 considered significant. We performed stepwise logistic regression analysis to examine factors associated with preexisting SBI. All variables with a P value less than 0.15 in univariate analysis were entered into the multivariate model. Odds ratios (OR) and 95% confidence intervals (CI) were calculated for each factor in the presence of the final model. Goodness of fit was assessed by the Hosmer–Lemeshow statistic. All statistical analyses were completed using the statistical package from SAS Institute (version 6.12; Cary, NC, USA).

Results

Of the 449 patients studied, 158 (35.2%) had SBI, 66 (14.7%) had BI, and 225 (50.1%) did not have any apparent infarctions on MRI. Multiple infarctions were more prevalent in patients with BI (59.1%) than in those with SBI (32.1%; $P < 0.001$). Patients with SBI and BI had infarctions, respectively, in the cerebral cortex (2.5% vs. 15.2%), subcortical white matter (27.2% vs. 18.2%), basal ganglia (66.5% vs. 65.2%), and cerebellum and/or brainstem (3.8% vs. 1.4%) (all $P = 0.004$).

Preoperative and intraoperative characteristics for all patients are summarized in Table 1. Patients with SBI were older and showed a higher prevalence of renal dysfunction compared to controls. Hypertension, AAA, severe intracranial artery stenosis, and severe carotid artery stenosis were significantly more common in patients with BI than in controls. Only hypertension was statistically significant in patients with BI compared to patients with SBI. There were no difference in other atherosclerotic factors between SBI and BI. To further clarify the relationship between age and SBI and BI, we stratified patients by MRI findings and age. Figure 1 shows that the prevalence of SBI gradually increased with age, from 22.7% in 60- to 64-year-old patients to 42.4% in the oldest (75–85 years old), whereas the incidence of BI decreased from 18.7% in 60- to 64-year-old patients to 15.2% in the oldest patients.

Preoperative and postoperative neurological conditions for all patients are shown in Table 2. Patients with SBI and BI had a higher prevalence of preoperative cognitive impairment and lower HDS scores than controls. POCD was significantly more frequent in patients with SBI and BI compared to controls. Postoperative stroke was seen statistically more often in patients with BI than in controls. The incidence of postoperative stroke also tended to be higher in patients with SBI compared to controls, although the difference was not significant. There were no statistically significant differences between SBI and BI patients among the variables shown in Table 2.

Analysis of preoperative characteristics by stepwise logistic regression identified age (OR per 10 years, 1.41; $P = 0.057$), renal dysfunction (OR 2.45; $P = 0.012$), preoperative cognitive impairment (OR 2.77; $P = 0.010$), atherosclerosis of the ascending aorta (OR 1.31; $P = 0.056$), and intracranial artery stenosis (OR 1.62; $P = 0.073$) to be associated with SBI (Table 3).

Discussion

Our results showed that the prevalence of postoperative neurological complications in patients with SBI was higher than in controls and less than in BI. Advanced age, renal dysfunction, and preoperative cognitive impairment were common in patients with SBI. Multivariate analysis showed that age, renal dysfunction, preoperative cognitive impairment, atherosclerosis of the ascending aorta, and intracranial arterial stenosis were associated with SBI.

Among our patients with SBI, 5.7% experienced postoperative stroke and 15.2% had POCD. The incidence of stroke after CABG is reported to be 1–3% of patients in most series [8–10], the same frequency as in our control patients. Postoperative stroke occurred more than four times more often in patients with SBI than in controls (1.3%), although not as frequently as in patients with BI (9.1%). We found that patients with SBI were at high risk of stroke after CABG. POCD has been reported to affect 20–30% of patients 1 month after cardiac surgery [11, 12]. POCD was found more frequently in our patients with SBI than in controls, although the incidence of POCD in SBI

Table 1 Preoperative and intraoperative characteristics by group

	Control ($n = 225$)	SBI ($n = 158$)	BI ($n = 66$)	P value
Age, years (mean ± standard deviation)	69.4 ± 5.4	70.9 ± 5.3[a]	69.9 ± 5.8	0.029
60–64	44 (20)	17 (11)	14 (21)	0.083
65–74	139 (62)	99 (63)	37 (56)	
≥75	42 (18)	42 (26)	15 (23)	
Gender (male/female)	157/68	99/59	52/14	0.052
Hypertension	145 (64)	101 (64)	53 (70)[bc]	0.038
Diabetes mellitus	81 (36)	53 (34)	22 (33)	0.854
Hyperlipidemia	108 (48)	69 (44)	35 (53)	0.417
Peripheral vascular disease	14 (6)	20 (13)	6 (9)	0.093
Abdominal aortic aneurysm	5 (2)	10 (6)	6 (9)[b]	0.032
Renal dysfunction (Cr ≥1.9 mg/dl)	15 (7)	24 (15)[a]	7 (11)	0.025
Smoking	135 (60)	79 (51)	42 (65)	0.075
MRA (carotid arteries)				
Normal or mild	210 (93)	141 (89)	53 (80)[b]	0.019
Moderate	6 (3)	7 (4)	3 (5)	
Severe or obstruction	9 (4)	10 (6)	10 (15)	
MRA (cerebral arteries)				
Normal or mild	201 (89)	130 (82)	44 (67)[b]	<0.001
Moderate	23 (10)	22 (14)	16 (24)	
Occluded	1 (1)	6 (4)	6 (9)	
Ascending aorta				
Normal or mild	175 (78)	103 (65)	45 (68)	0.054
Moderate	21 (9)	21 (13)	11 (17)	
Severe	29 (13)	34 (22)	10 (15)	
CPB time (min)	103.5 ± 24.0	104.2 ± 23.5	99.0 ± 24.9	0.313
Aortic clamp time (min)	67.9 ± 22.4	62.3 ± 28.4	60.7 ± 25.4	0.036

Values in parentheses represent percentages within the group

SBI silent brain infarction, *BI* symptomatic brain infarction, *Cr* creatinine, *MRA* magnetic resonance angiography, *CPB* cardiopulmonary bypass

[a] SBI different from control

[b] BI different from control

[c] BI different from SBI

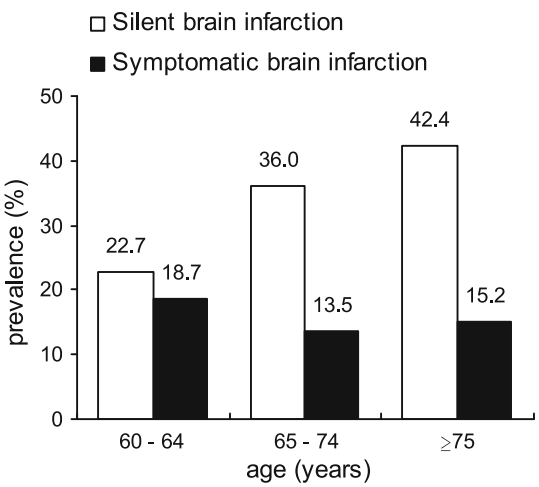

Fig. 1 Patients with silent brain infarction and symptomatic brain infarction by age (years)

and BI was lower than in other studies. We measured cognitive function using HDS, a modified MMSE and primarily measured attention and verbal memory. Therefore, the prevalence of POCD in our patients might be lower than in other studies. Further research on POCD may be needed, because the prevalence of POCD differs depending on the definition and methodological approaches to diagnosis [13].

In our study, almost half the patients (49.9%) who underwent CABG were classed as either SBI (35.2%) or BI (14.7%). This may indicate that atherosclerotic lesions in coronary arteries were commonly associated with cerebral vessel lesions. In the general population, the prevalence of SBI has been reported to range from 8% to 28% [6]. Age is a well-established risk factor for SBI, and the incidence of SBI significantly increased with age [7, 14]. The prevalence of SBI in each generation among our patients was

Table 2 Preoperative cognitive impairment and postoperative neurological complications by group

	Control ($n = 225$)	SBI ($n = 158$)	BI ($n = 66$)	P value
Preoperative cognitive impairment (HDS <24)	11 (5)	23 (15)[a]	16 (24)[b]	<0.001
Preoperative HDS score (mean ± standard deviation)	27.6 ± 2.1	26.3 ± 3.1[a]	25.3 ± 3.8[b]	<0.001
Postoperative cognitive dysfunction	11 (4.9)	24 (15.2)[a]	12 (18.2)[b]	0.003
Postoperative stroke	3 (1.3)	9 (5.7)	6 (9.1)[b]	0.008

Values in parentheses represent percentages within the group

SBI silent brain infarction, *BI* symptomatic brain infarction, *HDS* Hasegawa dementia scale

[a] SBI different from control

[b] BI different from control

Table 3 Stepwise multiple models to identify independent risk factors for SBI in patients undergoing CABG

	SBI vs. control odds ratio (95% CI)
Age	1.41 (0.99–2.01)
Renal dysfunction (Cr ≥1.9 mg/dl)	2.45 (1.22–4.94)
Preoperative cognitive impairment	2.77 (1.27–6.04)
Atherosclerosis of the ascending aorta	1.31 (0.99–2.74)
Intracranial arterial stenosis	1.62 (0.96–2.74)
Hosmer–Lemeshow GOF	0.940
Receiver operator character	0.648

SBI silent brain infarction, *BI* symptomatic brain infarction, *CABG* coronary artery bypass grafting, *CI* confidence interval, *Cr* creatinine, *GOF* goodness of fit

slightly higher than in other studies, where the average prevalence of SBI was approximately 6–7% at age 60 and increased to 28% at age 80 [7, 15–17]. We found that the prevalence of SBI increased gradually with age, a pattern not seen in BI (Fig. 1). We confirmed that SBI was more common in patients who underwent CABG than in healthy subjects and that the prevalence gradually increased with age.

Renal dysfunction was more prevalent in patients with SBI and was associated with SBI. Both the kidney and the brain are very low resistance end organs and are continually and passively perfused by high-volume blood flow throughout systole and diastole. Therefore, small vessels in the kidney and brain are highly susceptible to fluctuations in blood pressure and flow [18]. Because of these hemodynamic similarities between the vascular beds of the kidney and brain, small vessel disease in the kidney may indicate the presence of small vessel disease in the brain. Impaired kidney function has been reported to be associated with cerebral small vessel disease [19] and stroke [20]. These associations, found in our study and by others, may be explained by atherosclerosis that develops in the renal and cerebral vasculature. Because atherosclerosis could induce widespread inflammation and oxidative stress [21], patients with SBI might be vulnerable to surgical stress, especially as caused by CPB, and have an increased risk of postoperative neurological complications.

We found a relationship between atherosclerosis of the ascending aorta and SBI, which may reflect emboli from a ruptured or ulcerated atheroma in the ascending aorta in patients with SBI before surgery. Moreover, atherosclerosis of the ascending aorta has been demonstrated to be a risk factor for postoperative stroke after cardiac surgery [1–3]. Information from epiaortic ultrasound of the ascending aorta has a significant effect on surgical decision making in cardiac surgical patients and might improve postoperative neurological outcomes [22]. Although CPB was applied to all patients in our study, we might have to evaluate the difference in postoperative neurological complications between on- and off-pump CABG to assess embolic burden from the ascending aorta.

In contrast, carotid stenosis was more common in patients with BI than in controls in our study. Despite keeping mean arterial pressure at 50–70 mmHg for most patients and above 70 mmHg in patients with severe carotid stenosis or multiple infarctions to avoid cerebral hypoperfusion, the frequency of postoperative stroke and POCD was high in patients with SBI and BI. Gold et al. [23] found fewer neurological complications after CABG surgery when mean arterial pressure during CPB was between 80 and 100 mmHg rather than between 50 and 60 mmHg. Reduced cerebral blood flow during CPB might be a primary cause of ischemic brain injury, or it could exacerbate injury by impairing clearance of microemboli-sms [24]. Further studies should be performed to identify the optimal arterial blood pressure during CPB in patients with cerebral infarctions.

Stenosis of intracranial arteries was an independently associated factor for our patients with SBI. Whether it is symptomatic or not, the presence of infarctions may reflect cerebral vessel disease. Patients with BI had more cortical and multiple infarctions and carotid stenosis, which may cause apparent symptoms observed in patients with BI. We also determined that hypertension was more common in

patients with BI. Hypertension may lead to more severe progression of disease in cerebral vessels and produce multiple infarctions, which were demonstrated to be more frequent in patients with hypertension [25].

We found that preoperative cognitive impairment was common in patients with SBI and BI and was an independently associated factor for SBI. Infarctions found in SBI and BI were primarily located in the basal ganglia. The location of a lacuna might provide an explanation for preoperative cognitive impairment because lacunae in basal ganglia have been demonstrated to be a significant predictor of cognitive decline [26]. Preoperative cognitive impairment may reflect diffuse cerebral vascular lesions. SBI without apparent neurological symptoms might be identified by assessing cognitive impairment before surgery, although the prevalence of preoperative cognitive impairment was reported to be 35% of CABG surgery patients [27]. We defined preoperative cognitive impairment as a score less than 24 points on the HDS. However, it is unclear whether this score was appropriate to find SBI, although neurocognitive tests may detect SBI before surgery. Further research may determine an appropriate HDS score to detect SBI.

Our study had some limitations. First, the study was performed in a single institution. Thus, our institutional standards or patients might have biased the results. Second, definitions of renal dysfunction, preoperative cognitive impairment, and POCD differ among institutions. Renal dysfunction was arbitrarily defined as serum creatinine $\geq$1.9 mg/dl in our study. It might be better to use lower levels of serum creatinine to evaluate renal function for analysis. We measured cognitive status using the HDS, which primarily measures the cognitive domains of attention and memory. Several detailed neurocognitive tests might be needed to capture cognitive performance more adequately. Furthermore, we only examined postoperative cognitive status at one point. We might also have to focus on the long-term neurological outcome.

In conclusion, this study demonstrated that pre-existing SBI is common in patients who undergo CABG. Patients with SBI revealed a high prevalence of neurological complications after CABG compared to those without infarctions. Intracranial arterial stenosis and preoperative cognitive decline were associated with SBI, although patients with SBI were clinically asymptomatic. Neurocognitive tests may be important to predict SBI when cerebral imaging examination is not feasible. Further studies are needed to examine whether detecting SBI before CABG reduces neurological complications after CABG.

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