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Original Article

Status of Acute Stroke Practice in Patients with a Cardiac Implantable Electronic Device

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Although diagnostic and therapeutic strategies for acute stroke patients in Japan depend largely on magnetic resonance imaging (MRI), patients with cardiac implantable electronic devices (CIED) must still rely on computed tomography (CT). We retrospectively analyzed clinical and neuroimaging data of ischemic stroke patients with CIED treated at our hospital. Forty-five patients were enrolled in the study. Patients were divided into two groups according to whether corresponding lesions were detected (group A, n=21) or not detected (group B, n=24) by the first brain CT. We also evaluated in detail the clinical courses of patients who arrived at hospital within therapeutic time windows for recanalization therapy. Negative fresh infarct in the first CT was associated, though not significantly, with early onset-to-arrival time and subcortical white matter infarction. Five patients did not undergo recanalization therapy because their families did not agree to the procedure. The reasons for their lack of consent included inadequate information about the safety and efficacy of recanalization therapy because MRI could not be performed. Our study confirmed delayed detection of the corresponding lesion and undertreatment for acute stroke in patients with CIED.

Key words: stroke, cardiac implantable electronic device, computed tomography, magnetic resonance imaging

The number of patients with cardiac implantable electronic devices (CIED) in Japan is rapidly increasing (with 75,112 implantations performed in 2019) because of broad indications for pacing devices and increased life expectancy <Japan Arrhythmia Device Industry Association: https://www.jadia.or.jp/medical/crt-p.html, https://www.jadia.or.jp/medical/crt-d.html (accessed May 10, 2021.)>. Previously, CIED were considered an absolute contraindication to magnetic resonance imaging (MRI) because of the potentially life-threatening interactions between the devices and magnetic fields or high-frequency pulses. With the development of MRI-conditional CIED, MRI scans in patients with CIED are now routine in many hospitals [1]. However, most institutional safety protocols include several limitations regarding patient selection for MRI, leaving MRI unavailable to many acute stroke patients.

Although diagnostic and therapeutic strategies for acute stroke patients in Japan depend largely on MRI [2], patients with CIED must still rely on computed tomography (CT). Patients with CIED are thus at a potential disadvantage due to the resultant delay in the diagnosis of acute ischemic stroke. However, these issues have not been as well recognized in the field of

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cardiology, as they have in neurology.

In the present study, to investigate how CIED influence the diagnosis, recanalization therapy, and prognosis of acute ischemic stroke in patients with CIED, we retrospectively compared the cases of ischemic stroke patients with CIED in whom the corresponding lesions were or were not detected by the first brain CT.

Materials and Methods

This retrospective study was approved by the Institutional Review Board of Saitama Medical University International Medical Center (approval number: 15-053). Patients were not required to give informed consent to participate in the study because the analysis used anonymous clinical data that were obtained after each patient had provided written consent to treatment. Also, we applied an opt-out method to obtain consent for this study through an announcement on our hospital's website. The announcement was approved by the Institutional Review Board.

We retrospectively analyzed the clinical and neuroimaging data of acute ischemic stroke patients with CIED treated at our hospital between April 2007 (when the hospital opened) and March 2016. Acute ischemic stroke was defined as hospital arrival within 7 days of symptom onset. The data were obtained from electronic medical charts and summaries. We evaluated the patients' characteristics (age, sex), the causative arrhythmia, type of CIED, underlying stroke risk factors (atrial fibrillation, coronary artery disease, hypertension, diabetes mellitus, dyslipidemia, current smoking, prior stroke), echocardiographic findings, laboratory data (D-dimer, brain natriuretic peptide) on admission, and use of antithrombotic (antiplatelet and/or anticoagulant) agents before the index stroke.

We also evaluated the onset situation (awake or asleep), mode of arrival at the hospital, onset-to-arrival time, initial symptoms, National Institutes of Health Stroke Scale (NIHSS) score, stroke subtype, brain CT findings, functional outcome using the modified Rankin scale score [3] at discharge, and the duration of hospital stay. Stroke subtypes were defined according to the Trial of ORG 10172 in the Acute Stroke Treatment Subtype Classification [4].

All CT imaging was performed on a 64-row multidetector CT scanner (General Electric LightSpeed VCT system; GE Healthcare, Milwaukee, WI, USA). A standard axial CT of the whole brain was performed with a sequential technique for a 5-mm slice thickness. CT was used to identify the infarct in all patients, and infarct size was defined as follows: small, longest diameter ≤ 15 mm; large, infarct larger than one-third of the territory of the middle cerebral artery, anterior cerebral artery, posterior cerebral artery, or cerebellar hemisphere; all other sizes were classified as medium [5]. CT cerebral angiography was used in some patients. White matter lesions were classified on a scale of 0-3 according to their location and size by grade [6]. Patients were divided into 2 groups: those with fresh infarcts detected by the initial CT (group A) and those in whom fresh infarcts were not detected by the initial CT (group B). The therapeutic strategies did not differ between the groups. The protocol of recanalization therapy for hyperacute ischemic stroke patients with CIED at our institute was as follows: (i) noncontrast CT-based exclusion of symptomatic intracranial hemorrhage, (ii) CT angiography and/or perfusion CT was also performed if it would not unduly delay recanalization therapy.

In Japan, a recombinant tissue-type plasminogen activator (rt-PA) was approved in October 2005 for use within 3 h of stroke onset. In August 2012, the therapeutic time window was extended to within 4.5 h of symptom onset. To investigate how CIED influence acute recanalization therapy, we confirmed the clinical courses of patients who underwent recanalization therapy. For those who did not receive this therapy, we assessed the reason why. Our hypothesis was that the inability to diagnose a stroke using MRI could decrease the frequency of recanalization therapy.

Statistical analysis was performed using PASW statistical software (version 20; IBM Corp., Armonk, NY, USA). Wilcoxon's rank-sum test and Pearson's chi-square test were used to compare the characteristics between the groups.

Results

Forty-nine patients with CIED were admitted because of ischemic stroke, but we excluded 4 patients because they were diagnosed as having transient ischemic attacks. Therefore, the final study sample size was 45 patients. The patients included in this study represent 1.5% of the total number of patients (n = 2,997) with ischemic stroke admitted to our institution. The study flowchart is shown in Fig. 1. Corresponding lesions were detected in 21 patients (47%) on the initial CT (group A); 24 patients (53%) did not show corresponding lesions on the initial CT (group B). In group B, 2 patients had a hyperdense middle cerebral artery sign and 2 others had a middle cerebral artery dot sign. One patient underwent enhanced CT on admission, and corresponding vessel occlusion was confirmed. All patients underwent a second CT; fresh lesions were newly confirmed in 15 patients at a mean of 1.8 days after the first CT, and hypodense area expansion was confirmed in 7 patients at a mean of 4.1 days after the first CT. In group B, 2 patients experienced a 1-day delay in treatment because corresponding lesions were not detected on the first CT at the previous institutions.

The baseline characteristics of the patients in each group are listed in Table 1. There were no significant differences between the groups except for coronary artery disease. Stroke characteristics in the 2 groups are listed in Table 2. All patients arrived at hospital within 72 h of stroke onset. Onset-to-arrival time was longer in group A than in group B (median: 2.25 h versus 1 h, respectively; $p=0.266$). Two or more infarct locations were the most frequent in both groups, and almost all lesions were cerebral cortico-subcortical. Subcortical white matter was a more frequent location in group B than in group A (34% versus 5%, respectively; $p=0.101$), but the difference was not statistically significant. Although the ratio of good functional outcome at discharge (modified Rankin scale score: 0 or 1) was higher in group B (29%) than in group A (10%), the difference was not significant ($p=0.143$).

Onset-to-arrival time was within 4.5 h in 31 patients (69%), and in 2 of the 31 patients it was within 3-4.5 h (1 patient in each group). The characteristics of 4 patients (3 in group A and 1 in group B) treated with acute recanalization therapy are listed in Table 3. Two patients were treated with recanalization therapy based on CT only, without contrast enhancement. Intravenous rt-PA was effective in 1 patient, but cardioembolic stroke recurred during that patient's hospital stay. Symptomatic hemorrhagic transformation was seen in 1 patient. The effectiveness of recanalization therapy varied depending on the patient.

Twenty-seven patients did not undergo recanalization therapy despite their arrival within the therapeutic time windows. The most common reasons for not receiving rt-PA treatment were mild or rapid improvement in symptoms (n = 12), CT findings of major infarct signs (n = 6), lack of consent by the family (n = 5), active bleeding (n = 2), and prothrombin time/international normalized ratio > 1.7 (n = 2). Factors influencing the families' decisions to disagree rt-PA treatment included inadequate information regarding the safety and efficacy of rt-PA because MRI could not be performed. Without MRI, the sizes of the infarct and the occluded vessel remain speculative, thus hindering a family's ability to decide on this possibly harm-

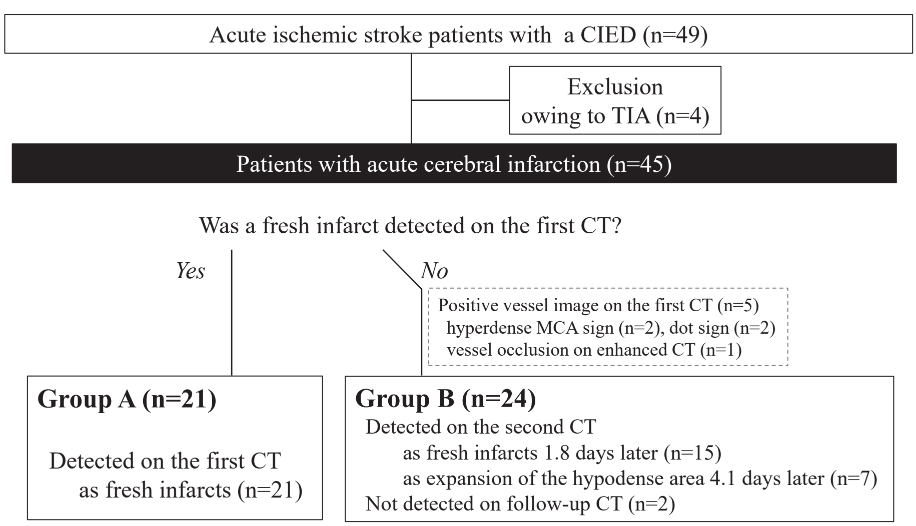

Fig. 1 Patient flowchart.
CIED, cardiac implantable electronic device; TIA, transient ischemic attack; CT, computed tomography; MCA, middle cerebral artery.

ful intervention. The characteristics of the 5 patients (1 in group A and 4 in group B) who did not undergo recanalization therapy due to family disagreement are listed in Table 4. All 5 of these patients had poor functional outcomes at discharge (modified Rankin scale score ≥ 5). Although 5 patients in this study had MRI-conditional CIED, brain MRI was not performed during the acute stroke phase in these patients.

Discussion

In less than half of the patients with CIED (47%), corresponding lesions were detected by the first CT without contrast enhancement. Accordingly, a delay in stroke treatment occurred in 2 patients (group B), but the functional outcomes did not differ between the patients in whom corresponding lesions were detected and those in whom they were not detected by the first CT. Previous studies showed that the sensitivity of CT in detecting cortical infarcts is relatively high because CT visualizes both density change and swelling, whereas the sensitivity of CT in identifying ischemic lesions is poor in patients with mild stroke (NIHSS < 4) or with small infarcts (< 1 mL) [8-10]. Although our study population included many patients who had cortical infarcts and moderate strokes (median NIHSS: 8 in group A and 9 in group B), the sensitivity of the first CT in identifying corresponding lesions did not reach

Table 1 Background characteristics of the patients with a cardiac implantable electronic device

	Group A: Detected on initial CT N = 21	Group B: Not detected on initial CT N = 24	*P*-value
Age (years)	78 ± 7	77 ± 13	0.945
Women (%)	8 (38)	11 (46)	0.764
Causative arrhythmias			1.000
SSS (%)	11 (52)	10 (42)	
AVB (%)	5 (24)	11 (46)	
Others (%)	5 (24)	3 (12)	
Type of CIED			0.608
pacemaker (%)	19 (90)	20 (84)	
ICD (%)	2 (10)	2 (8)	
CRT pacemaker (%)	0 (0)	1 (4)	
CRT defibrillator (%)	0 (0)	1 (4)	
Time since device implantation (years)	6.7 ± 8.7	6.7 ± 6.5	0.436
Stroke risk factors			
Atrial fibrillation (%)	12 (57)	13 (54)	1.000
Coronary artery disease (%)	1 (5)	9 (38)	0.010
Hypertension (%)	10 (48)	15 (63)	0.377
Diabetes mellitus (%)	3 (14)	4 (17)	1.000
Dyslipidemia (%)	3 (14)	6 (25)	0.469
Current smoking (%)	1 (5)	2 (8)	1.000
Prior stroke (%)	3 (14)	5 (21)	0.705
Echocardiographic findings			
Left atrial dimensions (mm)	42.5 ± 8.7	40.6 ± 7.7	0.349
Ejection fraction (%)	57 ± 14	62 ± 16	0.180
Laboratory data on admission			
D-dimer (μg/mL)	6.9 ± 22.5	3.6 ± 3.6	0.146
Brain natriuretic peptide (pg/mL)	854 ± 1,201	699 ± 371	0.374
Antithrombotic treatment			
Anticoagulant only (%)	3 (14)	6 (25)	0.469
Antiplatelet only (%)	8 (38)	9 (38)	1.000
Combined therapy (%)	1 (5)	2 (8)	1.000

AVB, atrioventricular block; CIED, cardiac implantable electronic devices; CRT, cardiac resynchronization therapy; CT, computed tomography; ICD, implantable cardioverter defibrillator; SSS, sick sinus syndrome. Date are given as mean ± standard deviation, or number (%).

Table 2 Stroke characteristics of the patients with a cardiac implantable electronic device

	Group A: Detected on initial CT N = 21	Group B: Not detected on initial CT N = 24	*P*-value
Onset situation, n (%)			1.000
awake	17 (81)	20 (83)	
asleep	4 (19)	4 (17)	
Method of transport to hospital, n (%)			0.351
ambulance	15 (71)	21 (88)	
walk-in	5 (24)	2 (8)	
in-hospital onset	1 (5)	1 (4)	
Onset-to-arrival time, hours	2.25 (1–11.75)	1 (1–2.75)	0.266
Initial symptoms, n (%)			
facial palsy	12 (57)	11 (46)	0.554
hemiparesis	18 (86)	18 (75)	0.469
speech impairment	15 (71)	15 (63)	0.752
NIHSS score on admission	8 (3–15)	9 (2–15)	0.882
Stroke subtype, n (%)			0.829
Cardioembolic	19 (90)	20 (83)	
Atherosclerotic	1 (5)	3 (13)	
Lacunar	1 (5)	1 (4)	
Stroke location, n (%)			0.101
Two or more infarct locations	16 (75)	13 (54)	
Cerebral cortex	1 (5)	0 (0)	
Subcortical white matter	1 (5)	8 (34)	
Basal ganglia	1 (5)	0 (0)	
Brainstem	1 (5)	0 (0)	
Cerebellum	1 (5)	1 (4)	
Invisible	0 (0)	2 (8)	
Stroke size, n (%)			0.166
Large	11 (52)	9 (38)	
Medium	9 (43)	9 (38)	
Small	1 (5)	6 (24)	
White matter lesion, grade	1 (0–2)	1 (0–2)	0.582
Outcomes			
mRS score at discharge	4 (3–5)	4.5 (1–5)	0.617
mRS score 0 and 1 at discharge, n (%)	2 (10)	7 (29)	0.143
Duration of hospital stay, days	35 (27–46)	29 (12.8–53)	0.495

CT, computed tomography; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale. Date are given as number (%), or median (interquartile range).

50%. Although MRI with diffusion-weighted images is more accurate than CT for diagnosing acute ischemic stroke [9-10], our present series of patients with CIED have not received the benefits of MRI yet. Although the prevalence of coronary artery disease was significantly higher in group A than in group B, the difference was probably attributable to the small sample size.

In our study, only 4 patients (3 in group A and 1 in group B) underwent recanalization therapy. It might be considered that patients in group B would be better candidates for recanalization therapy than those in group A, but actually it's not. Although recanalization therapy is effective and safe for ischemic stroke patients within 3 h after onset even with a CT-based diagnosis [11], undetection of corresponding lesions may have made physicians hesitate to choose recanalization therapy and thus led families not to agree to the treatment. Although it was reported that stroke physicians could choose recanalization therapy with more certainty in MRI-based patient selection than in CT-based patient selection [12], they need to choose CT-based recanalization therapy without hesitation in patients with CIED.

Table 3 Stroke characteristics of the patients treated with recanalization therapy

Patient, Group	1, A	2, A	3, A	4, B
Age, Sex	85, F	70, M	76, M	92, M
Onset-to-arrival time, hours	0.75	1	1	1
NIHSS on admission	20	21	13	9
Stroke subtype	Cardioembolic	Cardioembolic	Cardioembolic	Cardioembolic
Atrial fibrillation	+	—	+	—
ASPECT	9	9	8	10
Occluded artery	ICA	MCA	ICA	MCA
Diagnostic imaging	CT-Angiography, CT-Perfusion	CT-Perfusion	CT without contrast enhancement	CT without contrast enhancement
Recanalization therapy	rt-PA	rt-PA	rt-PA, EVT	rt-PA
Symptomatic hemorrhagic transformation	—	—	+	—
mRS score at discharge	5[#]	2	4	4

[#] Intravenous rt-PA was effective in patient 1, but cardioembolic stroke recurred during hospital stay.
ASPECT, Alberta Stroke Program Early CT Score [7]; CT, computed tomography; EVT, endovascular therapy; F, female; ICA, internal carotid artery; NIHSS, National Institutes of Health Stroke Scale score; M, male; MCA, middle cerebral artery; mRS, modified Rankin Scale; rt-PA, recombinant tissue-type plasminogen activator.

Table 4 Stroke characteristics of the patients untreated with recanalization therapy for family disagreement

Patient, Group	1, A	2, B	3, B	4, B	5, B
Age, Sex	81, M	76, F	81, M	81, F	79, F
Onset-to-arrival time, hours	1	1	2	1	3.5
NIHSS on admission	15	27	21	11	21
Stroke subtype	Cardioembolic	Atherothrombotic	Cardioembolic	Atherothrombotic	Cardioembolic
Atrial fibrillation	—	—	+	—	—
mRS score at discharge	5	5	6	5	5

M, male; F, female; NIHSS, National Institutes of Health Stroke Scale score; mRS, modified Rankin Scale.

In a previous report, MRI-required events after CIED implantation cumulatively increased at the rate of 5.3% per year [13]. Among such events, intracranial disease was the most frequent, accounting for 43% of the total events [13]. MRI examinations in patients with CIED require special attention as well as several steps from the referring stroke department along with the radiology and cardiology departments. It would be better for each hospital to establish a protocol to promptly perform MRI for acute stroke patients with CIED, though only the minimum imaging examination (*e.g.*, CT without contrast enhancement) is required by Japanese guidelines for intravenous rt-PA [2].

This study had several limitations. First, this was a single-center, retrospective study. Second, the number of patients was small, and they were followed up only during their hospital stay. In some patients, functional outcomes may recover after discharge. Third, we did not compare stroke characteristics between patients with and those without CIED.

Our study confirmed the delayed detection of the corresponding lesion in patients with CIED. Although intravenous rt-PA is an approved treatment for acute ischemic stroke within 4.5 h of symptom onset [2], patients with CIED are still left undertreated because of the inability to reach a diagnosis using MRI. Although better functional outcomes were expected in group B than in group A because of the earlier onset-to-arrival time in group B patients, functional outcomes did not differ between the 2 groups. We speculate that the inability to diagnose with MRI caused a delay or hesitation in acute stroke treatment, leading to poorer functional outcomes in some patients. Recently, MRI-conditional CIED has been clinically introduced, and this may be desired to create an environment in which patients with CIED receive the benefits of MRI in acute stroke practice.

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