Treatment Outcome Using Insertable Cardiac Monitoring in Patients with Cryptogenic Stroke after Thrombectomy

Ryosuke Doijiri,¹ Naoto Kimura,² Ken Takahashi,¹ Hideaki Endo,³ Michiko Yokosawa,² Hiroaki Takahashi,¹ Takayuki Sugawara,² and Takahiko Kikuchi¹

Objective: Insertable cardiac monitoring (ICM) systems are useful for diagnosing paroxysmal atrial fibrillation (PAF) in cryptogenic stroke (CS). We assessed the initial treatment outcome using insertable cardiac monitors in CS treated by endovascular reperfusion therapy.

Methods: Of 102 consecutive acute ischemic stroke patients with large vessel occlusion (LVO) treated by endovascular therapy, we included 10 with CS who underwent insertable cardiac monitor placement between December 2016 and June 2018 at our hospital. Atrial fibrillation (AF) was determined by performing screening tests such as 12-lead electrocardiography (ECG), Holter ECG, and continued electrocardiographic monitoring for 3 days. Transesophageal echocardiogram (TEE) was essential to diagnose CS. We analyzed the parameters of AF and the time at which AF was first detected within 1 year.

Results: There were eight (80%) male patients, and the median age was 68 (interquartile range [IQR]: 59–76) years. The parameters of AF were not outliers. The detection rate of AF at 12 months was 60%. The median time from onset of stroke to device insertion was 17 (range: 10–22) days, and the median time from device insertion to detection of the first AF episode was 52 (range: 12–344) days.

Conclusion: The detection rate of AF in acute ischemic stroke patients with LVO treated by endovascular therapy was higher than that in previous reports.

Keywords ▶ insertable cardiac monitors, cryptogenic stroke, large vessel occlusion, paroxysmal atrial fibrillation

Introduction

Insertable cardiac monitoring (ICM) for cryptogenic stroke (CS) has been approved. The incidence of CS based on the Trial Org 10172 in Acute Stroke Treatment (TOAST) classification was 16%–39%.¹ As an etiological factor for CS, latent atrial fibrillation (AF) has been emphasized, and a previous study demonstrated the difficulty of identifying it using Holter electrocardiography (ECG).² In the cryptogenic stroke and underlying atrial fibrillation (CRYSTAL AF) study, paroxysmal atrial fibrillation (PAF) was detected in 30% of the patients in the ICM group during a period of 3 years, suggesting the usefulness of ICM.² Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke trials (HERMES) collaborators who suggested the efficacy of thrombectomy reported that 33% of the patients had a history of AF³; AF may have been present in patients with large vessel occlusion (LVO). However, the detection rate of PAF on ICM in CS patients with LVO is unclear. We examined the detection rate of PAF in CS patients with LVO, assuming it to be high.

Materials and Methods

The subjects were 102 patients with acute cerebral infarction who were admitted to our hospital between December 2016 and June 2018, and on whom thrombectomy was
Table 1

<table>
<thead>
<tr>
<th>Cerebrovascular Disease</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiogenic cerebral embolism</td>
<td>67 (65%)</td>
</tr>
<tr>
<td>Atherothrombotic cerebral infarction</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Trousseau syndrome</td>
<td>11 (1%)</td>
</tr>
<tr>
<td>Aortogenic cerebral embolism</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Cerebral artery dissection</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

ICM implantation n=20 (20%)

Fig. 1 The study flow is presented. Of 102 patients with acute cerebral infarction who underwent thrombectomy, the subjects were 15 with cryptogenic stroke, excluding those with cardiogenic cerebral embolism, atherothrombotic cerebral infarction, Trousseau syndrome, aortogenic cerebral embolism, or cerebral artery dissection. ICM: insertable cardiac monitoring performed. They consisted of 67 (65%) with cardiogenic cerebral embolism, 11 (11%) with atherothrombotic cerebral infarction, 2 (2%) with Trousseau syndrome, 1 (1%) with aortogenic cerebral embolism, 1 (1%) with cerebral artery dissection, and 20 (20%) with CS (Fig. 1). Of the 20 patients with CS, ICM was performed on 10 (10%) according to the guidelines for the diagnosis of CS patients for whom an ICM device may be indicated. A diagnosis of CS was made in accordance with the same guidelines. Necessary items described in the guidelines (cerebral MRI, 12-lead ECG, electrocardiographic monitoring for ≥24 hours, transthoracic echocardiography, diagnostic imaging of the carotid artery, and diagnostic imaging of the intracranial arteries were conducted for all patients. Transesophageal echocardiography (TEE) was performed on all patients. When a right to left shunt was present, ultrasonography of lower limb veins was conducted, and patients definitively diagnosed with cardiogenic, aortogenic, or paradoxical cerebral embolism were excluded. Exclusion criteria included patients definitively diagnosed with cerebral infarction related to large/small vessel occlusion or other etiological factors according to the TOAST classification. Electrocardiographic monitoring was conducted for ≥3 days. Blood coagulation tests for investigating specific etiological factors that may cause cerebral infarction were performed only for patients with a family history or relatively young patients. In all patients, neurologists implanted ICM devices under cardiologists’ guidance in the angiography room. Implantation was conducted according to the procedures described in the package inserts of the ICM device Reveal LINQ (Medtronic Inc., Minneapolis, MN, USA). After implantation, the position of the ICM device was confirmed under fluoroscopy using a frontal X-ray tube in the angiography room. After insertion, neurologists and clinical engineers confirmed the data via the Internet through personal computers at appropriate times using a remote monitoring system (CareLink, Medtronic Inc.). When PAF was detected, patients were requested to visit our hospital by telephone, and data on long-hour waveforms were collected using a CareLink 2090 Programmer (Medtronic Inc.) or CareLink Express (Medtronic Inc.). As a rule, we requested physicians specializing in arrhythmia to confirm the diagnosis of PAF. When a diagnosis of PAF was made, the secondary prophylactic drug was switched to a direct oral anticoagulant (DOAC) as a rule. When symptoms, such as palpitation, were present on PAF, patients were referred to physicians specializing in arrhythmia to assess the indications of drug therapy or catheter ablation. A procedure using a Penumbra aspiration catheter (Penumbra Inc., Alameda, CA, USA) and stent-type devices for thrombectomy (Solitaire FR: Medtronic; Trevo XP: Stryker Neurovascular, Fremont, CA, USA; Revive: Codman, Johnson & Johnson, Miami, FL, USA) was defined as thrombectomy. Clinical parameters were expressed as the median (interquartile range [IQR]) (number [%]). Regarding the date of device insertion as day 0, survival analyses were conducted. All data were analyzed using JMP version 12.0.1 software (SAS Institute, Cary, NC, USA).

Results

The patient background is shown in Table 1. The median age was 68 years (range: 59–76 years). There were eight males (80%). Regarding PAF-associated parameters, the median brain natriuretic peptide (BNP) level, D-dimer level, premature atrial contractions on Holter ECG, and left atrial appendage blood flow velocity at the time of outflow/inflow on TEE were 29 (8.8–56) pg/mL, 0.69 (0.62–0.78) pg/mL, 6 (2–129) beats/day, and 69 (57–96)/63 (48–64) cm/s, respectively. There were no significant abnormal findings other than a slight increase in the BNP level (Table 1). The median Congestive heart failure/LV dysfunction, Hypertension, Age ≥75y, Diabetes mellitus, Stroke/TIA (CHADS$_2$) score was 3 (2.75–3.25) and the median National Institutes of Health Stroke Scale (NIHSS) score was 15 (9–21). Of 10 patients in whom an ICM device was inserted, the median interval from the onset of cerebral infarction until ICM device insertion was 17 (10–22) days. In all patients, the device was inserted during admission due to acute-phase cerebral infarction. The internal carotid artery was occluded in two patients (20%), the proximal middle cerebral artery in
two (20%), the distal middle cerebral artery in two (20%), the M2 middle cerebral artery in three (30%), and the basilar artery in one patient (10%); occlusion of the internal carotid or middle cerebral arteries was frequently observed. The frequency of passing a stent-type device for thrombectomy was once in eight patients (80%). Effective recanalization (thrombolysis in cerebral infarction [TICI] classification: 2b and 3) was achieved in 10 patients (100%). In six patients (60%), PAF was detected within 1 year after insertion. Of these patients, the interval until PAF detection was ≤1 month in 3, 187 days in 1, 318 days in 1, and 421 days in 1. The median interval from implantation until PAF detection was 52 (12–344) days (Fig. 2). For all six patients in whom PAF was detected, Warfarin had been used as a secondary prophylactic drug for cerebral infarction, but it was switched to a DOAC. Catheter ablation was performed for three (50%) of the six patients. In one, the maximum R-wave value after insertion was <0.2 mV, requiring additional insertion. However, there were no other complications on or after insertion. Monitoring was conducted by neurologists using a remote monitoring system (CareLink). When PAF was detected, the secondary prophylactic drug was changed to a DOAC at the outpatient clinic by contacting the patients or their families.

**Discussion**

In this study, the detection rate of PAF on ICM in CS patients after thrombectomy was 60%. Furthermore, the TICI 2b-3 recanalization rate was 100%. The number of passing a stent-type device for thrombectomy was one in 80%, suggesting that thrombectomy was relatively simple. As an etiological factor for CS, latent AF has been emphasized. On March 22, 2016, the use of an ICM device...
in patients with CS was pharmaceutically approved. The detection rate of latent AF increases with prolongation of the measurement time. According to a previous study, AF was newly detected in 7.7%, 5.1%, 10.7%, and 16.9%, respectively, through sequential sessions of measurement in 4 phases: “ECG on the initial consultation,” “electrocardiographic monitoring/Holter ECG during admission,” “monitoring with a portable Holter ECG at the outpatient clinic,” and “outpatient telemetry/extracorporeal setting-type recorder/ICM”; latent AF was identified in 23.7% of the patients through four phases, suggesting the importance of long-term monitoring. In this study, the maximum observation period was 421 days (approximately 1 year), being shorter than that in previous studies using ICM. The CRYSTAL AF study reported a detection rate of PAF on ICM within 3 months in CS patients of 12%. The REVEAL AF study reported detection rates within 30 days and 6 months of 6.2% and 20.4%, respectively. According to Poli et al., the detection rate within 6 months was 28%, and Cotter et al. reported a detection rate of 25.5%, with a mean interval of 229 days from the onset of CS until PAF detection. Ritter et al. reported that the detection rate within 1 year was 16.7%, and Etgen et al. reported a detection rate of 27.3% within 5 months. According to Rojo-Martinez et al. and the Stroke Prior to Diagnosis of Atrial Fibrillation Using Longterm Observation With Implantable Cardiac Monitoring Apparatus Reveal (SURPRISE) study, the percentages were 33.7% and 16.1%, respectively, with a mean interval of 281 and 569 days from the onset of CS until PAF detection, respectively. In Japan, the “Guidelines for the diagnosis of cryptogenic stroke patients for whom an insertable cardiac monitoring device may be indicated” were prepared by the Japanese Stroke Society. In the guidelines, diagnostic procedures for CS patients are described in detail. In this study, PAF was detected within 1 year in 40% of CS patients in whom an ICM device was inserted at our hospital in accordance with the guidelines. This percentage was higher than that previously reported.

Recently, many clinical studies have reported the detection rate of PAF in embolic stroke of undetermined source (ESUS) patients, but few studies have examined the frequency or detection rate of PAF in ESUS patients with LVO. A meta-analysis of five clinical studies (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands [MR CLEAN], Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times [ESCAPE], Randomized Trial of Revascularization With Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset [REVASCAT], Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke [SWIFT PRIME], and Extending the Time for Thrombolysis in Emergency Neurological Deficits-Intra-Arterial [EXTEND-IA]) comparing thrombectomy with medical treatment in patients with acute LVO (HERMES collaborators) demonstrated that 33% of all patients had a history of AF; therefore, PAF may be present in stroke patients with acute LVO. Furthermore, in this study, the median interval from the onset of cerebral infarction until ICM device implantation was 17 (10–22) days; implantation was conducted relatively early. Carrazco et al. reported that the median interval until the detection of PAF was 34 (0–514) days, with a mean interval of 4.2 ± 2.6 days from admission until ICM device implantation, and that the detection rate of PAF within 18 months was 31%. These results suggest that the detection rate of PAF increases if the interval from the onset of cerebral infarction until ICM device implantation is short. In this study, implantation was performed in the early phase, as previously reported, and the detection rate of PAF was high. However, this may have been related to thrombectomy regardless of the timing of implantation.

This study has four limitations. First, the number of patients was limited. Second, this was a retrospective study involving a small number of patients. Third, the follow-up period was short. Fourth, the use of ICM devices increased the cost. In the future, long-term follow-up should be conducted for a larger number of patients.

### Conclusion

The detection rate of PAF on ICM in CS patients who were treated by endovascular therapy at our hospital was approximately 60% within a year, being higher than that previously reported. An ICM device should be positively used to detect PAF in CS patients after thrombectomy.

### Disclosure Statement

None of the first and co-authors have conflicts of interest to be disclosed concerning this report.
# References


