Utility of Duranta, a wireless patch-type electrocardiographic monitoring system developed in Japan, in detecting covert atrial fibrillation in patients with cryptogenic stroke

A case report

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Abstract

Rationale: Subcutaneous implantable electrocardiographs are highly effective in detecting covert atrial fibrillation (AF) in cryptogenic stroke. However, these invasive devices are not indicated for all cryptogenic stroke patients, and noninvasive improvements over conventional Holter-type ambulatory electrocardiography are needed. We evaluated the clinical application and effectiveness of Duranta (ImageONE Co., Ltd.), a wireless patch-type electrocardiographic monitoring system developed in Japan for chronically ill patients or home-based patients at the end of life. A Duranta device was used to detect covert AF in patients with acute ischemic stroke of undetermined source with no sign of AF during cardiographic monitoring ≥24 hours postadmission.

Patient concerns: A 72-year-old man with severe aortic stenosis was admitted to our hospital with dysarthria and right upper limb weakness. Diffusion-weighted plain head magnetic resonance imaging (MRI) showed acute cerebral infarctions across the left middle cerebral artery territory. Twelve-lead electrocardiography, Holter-type ambulatory electrocardiography, and cardiographic monitoring for ≥24 hours revealed no AF, indicating a probable diagnosis of artery-to-artery embolism following left common carotid artery stenosis detected by carotid ultrasound imaging and cerebral angiography.

Interventions: However, because of high blood brain natriuretic peptide (BNP) and valvular heart disease, continuous monitoring using Duranta was performed from the 2nd to 13th days after onset to exclude possible cardioembolic stroke. Waveform and heart rate trend graph analysis showed paroxysmal AF (PAF) occurred on the 5th and 9th days after onset. PAF did not occur at any other time during the observation period. The quality of the cardiograms sufficed for analysis and diagnosis of AF. The lightweight compact device can be placed quickly with no movement restriction. These features and our findings show the usefulness of the Duranta device for long-term continuous monitoring.

Lessons: A noninvasive wireless patch-type electrocardiographic monitoring system, Duranta, placed at the precordium, was useful in detecting covert AF in cryptogenic stroke patients, warranting further investigation.

Abbreviations: AF = atrial fibrillation, BNP = brain natriuretic peptide, CT = computed tomography, ESUS = embolic stroke of undetermined source, ID = identification, MRA = magnetic resonance angiography, NASCET = North American Symptomatic Carotid Endarterectomy Trial, NIHSS = National Institute of Health Stroke Scale, NINDS = National Institute of Neurological Disorders and Stroke, PAC = premature atrial contraction, PAF = paroxysmal atrial fibrillation, PC = personal computer, PVC = premature ventricular contraction, TOAST = Trial of Org 10172 in Acute Stroke Treatment.

Keywords: a wireless patch-type electrocardiographic monitoring system, covert atrial fibrillation, cryptogenic stroke, Duranta, noninvasive method
1. Introduction

Antithrombotic therapy for ischemic stroke varies depending on its clinical subtypes. For example, Japanese guidelines for treatment of stroke recommend the use of anticoagulant therapy for cardioembolic stroke, and antiplatelet therapy for non-cardioembolic stroke.[1,2] This means that careful consideration is required when diagnosing subtypes, but differentiating cardiogenic from noncardiogenic sources of cerebral embolism is often particularly difficult. Covert atrial fibrillation (AF) cannot be proven by routine examination when major subjective symptoms are absent, and subsequently, is often diagnosed as artery-to-artery embolism, or, because the source is undetermined, as cryptogenic stroke that accounts for approximately 25% of ischemic stroke cases.[3,4]

Covert AF is a likely of embolic source in many cases of cryptogenic stroke. Electrocardiographic devices enabling long-duration recording, such as patch-type or belt-type wearable devices developed mainly in Europe and North America, and subcutaneous implantable devices, have been introduced for the detection of covert AF in order to reduce the number of such cases; the CRYSTAL-AF study and the EMBRAC study showed that detection rates of covert AF increased as the electrocardiographic monitoring time after onset of cerebral embolism became longer.[3–15]

Nevertheless, only a few remote monitoring devices for long-duration electrocardiography are available in Japan, including Duranta (ImageONE Co., Ltd., Tokyo, Japan), a wireless patch-type electrocardiographic monitoring system developed and commercialized for medical use, which is placed on the chest.[16] Considering that subcutaneous implantable devices are invasive, and consequently not indicated for all patients with cryptogenic stroke, there is a high demand for noninvasive methods that perform better than the Holter-type ambulatory electrocardiography in detecting covert AF.

From December 2015, we started to employ Duranta, a medical-use device developed in Japan for monitoring of patients,[16] to detect covert AF during the acute phase of embolic stroke of undetermined source (ESUS) as a prospective clinical study. Subjects were patients in the acute phase of ESUS, who were admitted to our hospital within 24 hours after onset from December 2015 onward, and whose results of both 12-lead electrocardiography and electrocardiographic monitoring for ≥24 hours performed after hospitalization did not indicate AF. Exclusion criteria used were patients with: lacunar infarction, atherothrombotic cerebral infarction, history of obvious AF and valvular heart disease that would be a source of emboli, problems (e.g., precordial skin lesions) prohibiting attachment of the device, and other contraindications determined by physicians. A noninvasive wireless patch-type electrocardiographic monitoring system Duranta (Medical device certificate number 226ABZ0X0055000), developed in Japan, was placed in a precordial position during hospitalization (maximum 1 month) in order to detect covert AF.

Duranta, developed originally for home-based medical care and monitoring of patients at nursing homes, is a telemetry transmitter that transmits electrocardiographic waveform data to the cloud server via iPhone.[16] This single dipole electrocardiograph [78.4 mm (width) × 35.1 mm (depth) × 14.7 mm (thickness)] weighs 35 g, has a sampling frequency of 160 Hz, and transmits electrocardiographic waveform data for 7 consecutive days, or up to 10 days with a built-in lithium battery. The main body of the device was placed with a pair of BlueSensor P electrode pads (Ambu A/S, Ballerup, Denmark, Medical device certificate number 13B2X0017000001) in a precordial position in a NASA induction arrangement. An electrocardiography recording was started immediately after the main switch was turned on, and recorded waveform data were sent to the nearby iPhone through Bluetooth, and further to the cloud server via a 3G/4G/LTE/Wi-Fi network. Access to the cloud server was restricted with the use of a personal ID/password. Acquired real-time waveform data were accessible from iPhone (Apple Inc., CA, United States)/iPad (Apple Inc., CA, United States)/Windows PC (Thirdwave Diginnos Co., Ltd., Tokyo, Japan) for heart rate variability and other analyses (Figs. 1 and 2). The R position of the each electrocardiographic waveform is detected by Fast Fourier Transform waveform analysis. R-R interval is calculated from the R position detected and converted to heart rate. The viewer has graph to show that heart rate timeline (heart rate trend graph). The viewer shows the following graphs: first one is compressed heart rate trend graph of the day (Fig. 2), and second one is heart rate trend graph (Fig. 1). Like the ordinal 24-hours Holter ambulatory electrocardiography, physician can see the possibility of premature atrial contraction (PAC), premature ventricular contraction (PVC), and AF including PAF by compressed heart rate trend graph of the day (Fig. 2), but not enough information. AF-viewer shows 2 and 1/2 hours of heart rate trend as heart rate trend graph at once (Fig. 1), and physician can see not only possibility but the frequency of the arrhythmia such as PAC, PVC, and AF. When the user click the interest point on the heart rate trend graph (Fig. 1), the viewer shows the electrocardiographic waveform data around the time, and then, physician can diagnose the type of arrhythmia.

In this time, we demonstrate a case report of our prospective clinical study patients, in which Duranta device, a long-term continuous monitoring system, originally developed in Japan, showed its usefulness in detecting covert AF as embolic source in patients with cryptogenic stroke.

The study was approved by the Human Research Ethics Committee of St. Marianna University Hospital (No. 3025). Written informed consent was obtained from all patients or their families prior to participation in the study.

2. Case presentation

The patient was a 72-year-old man with chief complaints of dysarthria and right upper limb weakness. He underwent surgery for testicular seminoma at the age of 29 years, and had pneumonia at the age of 65 years. His medical history included hypertension requiring oral Zacras (containing 20 mg of azilsartan and 5 mg of amlopidine, 2 tablets, once daily in the morning), severe aortic stenosis, mild-to-moderate aortic regurgitation, glaucoma, and motor paralysis of the left upper limb after radiotherapy (details unknown). He was an occasional drinker and had quit smoking 6 years before onset (prior to that, he smoked 10 cigarettes/day for ≥50 years). He suddenly felt weakness of the right upper limb while washing his face around 6:30 am in the morning of March 9, 2016. He went to work with the condition persisting, and dysarthria was pointed out by a colleague around at 8:00 am that same day. He visited our hospital because neither of his symptoms had abated. Vital signs on admission were as follows: blood pressure, 153/83 mmHg; heart rate, 77/min, regular; body temperature, 36.2 °C; SpO₂, 98% (room air). General examination revealed a systolic ejection murmur (Levine scale III) at the right edge of the sternum. The
The patient was conscious and alert, and right upper limb weakness was not present based on a neurological examination. Other neurological findings included dysarthria, already known motor paralysis (manual muscle test score 2/5) and sensory impairment of the left upper limb, and right upper limb hyperreflexia. The National Institute of Health Stroke Scale (NIHSS) score was 5. Chest radiography detected mild cardiomegaly (cardiothoracic ratio of 51.4%), but there were no signs of pulmonary congestion or aortic arch calcification. Twelve-lead electrocardiography showed sinus rhythm with a heart rate of 83/min. Neither Holter-type ambulatory electrocardiography performed on the 2nd day after hospitalization nor ≥24-hours inpatient cardiography confirmed AF. Biochemical tests of a blood specimen showed a slightly elevated D-dimer level (1.0 µg/mL; normal level, <0.5 µg/mL), and an abnormally high brain natriuretic peptide (BNP) level (575.0 pg/mL; normal range, 0–18.4 pg/mL). Plain head computed tomography (CT) revealed bilateral cerebral atrophy, but did not indicate intracranial disease. Plain head magnetic resonance imaging (MRI) showed acute cerebral infarctions in slightly varying phases across the territory of the left middle cerebral artery as high-intensity and low-intensity areas in the cortex of the frontal lobe, the corona radiata, the precentral gyrus, and the subcortex of the parietal lobe on diffusion-weighted images and apparent diffusion coefficient maps, respectively. Head magnetic resonance angiography (MRA) did not depict disturbance of major intracranial arteries, and images suggested cerebral infarcts had developed through an embolic mechanism (Fig. 3). Continuous unfractionated heparin infusion therapy (10,000 units/day) was started, and carotid ultrasound imaging, performed in search of a source of emboli.
Figure 2. Analysis of compressed heart rate trend graph recorded with Duranta. Twelve-day continuous monitoring using a wearable Duranta revealed PAF in a patient with an unknown source of emboli. Data transmission was disrupted several times during the observation period because the data-transmitting iPhone was left uncharged or was carried out of range. Wireless communication was automatically re-established as soon as the iPhone was moved to within the working range, and data transmission was re-started automatically. Data were sent to the cloud server in real time, enabling daily, and hourly analysis. Compressed heart rate trend graph analysis confirmed multiple supraventricular premature contractions on the 3rd day after onset, PAF which persisted for approximately 8 hours occurred on the 5th day after onset, and another PAF which lasted at least 24 hours occurred on the 9th day after onset. PAF did not occur at any other time during the observation period (ended on the 13th day after onset). PAF = paroxysmal atrial fibrillation.
revealed wall irregularities accompanied with partial ulceration. Signs of severe stenosis of the left common carotid artery (82.6% based on the area method, peak systolic blood flow velocity of 195.1 cm/s at the site of stenosis) were also observed, which were consistent with post-radiotherapy findings (Fig. 4). Transthoracic echocardiography confirmed severe aortic stenosis and mild-to-moderate aortic regurgitation: the left atrial dimension was enlarged (46 mm), while the left ventricular ejection fraction (60%) and the left ventricular fractional shortening (32%) were within the normal range. An intracardiac thrombus and a patent foramen ovale were absent. Transesophageal echocardiography was not performed. Cerebral angiography confirmed stenosis of the left common carotid artery (60% by the North American Symptomatic Carotid Endarterectomy Trial [NASCET] method) (Fig. 5).

Taken together, these findings suggested a likely diagnosis of embolism restricted to within the left middle cerebral artery territory caused by an artery-to-artery embolus attributed to stenosis of the left common carotid artery. Nevertheless, based on the high blood BNP level and the presence of heart valve disease in the patient, continuous electrocardiographic monitoring using Duranta was performed from the 2nd to 13th days after onset to eliminate the possibility of cardioembolic stroke. Waveform and heart rate trend graph analyses revealed multiple supraventricular contractions on the 3rd day after onset, PAF lasting approximately 8 hours occurred on the 5th day after onset, and another PAF persisting for at least 24 hours occurred on the 9th day after onset. PAF did not occur at any other time during the observation period (Fig. 2). Because covert AF was detected, combination therapy with an anticoagulant (edoxaban 60 mg per day) and an antiplatelet agent (clopidogrel 75 mg per day) was started to prevent recurrence. The risk of hemorrhagic complications was seriously taken into consideration. The patient remained recurrence-free, and was discharged home after the 18th day of hospitalization.

3. Utility and problems of Duranta

Similar to the routinely used 24-hours Holter-type electrocardiograph, Duranta produced waveforms of a quality high enough for the diagnosis of AF and other analysis. Furthermore, levels of motion artifacts due to body movements such as those during rehabilitation were low because that; firstly, Duranta is placed on the sternum at the center of the chest, so that the efficiency of muscle noise is almost none. Secondly, Duranta does not have any leads and it makes free from the noise coming from the cables that 24-hours Holter ambulatory electrocardiography usually has. This compact device, weighing only 35 g, is easy to place on
Antithrombotic treatment strategies for ischemic stroke vary greatly depending on its clinical subtypes. According to the “2015 Japanese guidelines for treatment of stroke,” anticoagulant therapy with a direct oral anticoagulant or warfarin was recommended for cardioembolic stroke on the basis that nonvalvular AF is a common cause (Grade B), while antiplatelet therapy, rather than anticoagulant therapy, was strongly recommended for noncardioembolic stroke (Grade A), and for lacunar infarction (Grade B).11,12

Regarding the classification of clinical subtypes, those by the National Institute of Neurological Disorders and Stroke (NINDS),17 and the Trial of Org 10172 in Acute Stroke Treatment (TOAST)18 were recommended, and subtypes that are not classified into “atherothrombotic,” “cardioembolic,” or “lacunar” infarction were categorized as “other types” in the NINDS, or “stroke of other determined etiology” and “stroke of undetermined etiology” in the TOAST classifications, respective-

ly. Such subtypes, of which cause remains undetermined even after sufficient examination are called “cryptogenic stroke,” and are thought to account for approximately 25% of all stroke cases.19-21 Moreover, many cryptogenic stroke cases are assumed to be cerebral embolism caused by covert AF,18,19 and whether or not covert AF is detected makes a considerable difference in therapy plans.

For detecting covert AF, electrocardiographic monitoring for at least 24 hours is recommended. However, the most effective period and method for monitoring has not yet been established. Also, one problem is that short-term Holter-type ambulatory electrocardiography, which is frequently used in clinical settings, underestimates the presence of covert AF. Due to the lack of clarity as to the standard of the extent of examination, a global working group comprising neurologists recently proposed a novel and clearer concept with a higher clinical value, namely “ESUS.”24

In this case, plain head MRI and MRA detected cryptogenic focal cerebral infarctions involving the cortex of the left frontal lobe in the left middle cerebral artery territory, but did not show an obvious occlusion of the major intracranial arteries, suggesting an embolic mechanism. To distinguish between cardioembolic or artery-to-artery embolic sources, we used common methods including 12-lead electrocardiography, ≥24-hours electrocardiographic monitoring, 24-hours Holter ambulatory electrocardiography, carotid ultrasound imaging, and transesophageal echocardiography. As a result, ≥50% stenosis and ulcer formation in the left common carotid artery was found, suggesting that an artery-to-artery source was most likely. However, the possibility of a cardiogenic source could not be eliminated given the underlying severe aortic stenosis and high blood BNP levels. Thus, long-duration continuous electrocardiographic monitoring was performed using Duranta. This detected covert AF at least twice during the monitoring period, indicating both artery-to-artery and cardioembolic sources. Based on these findings, categorization of the stroke was not possible in the present case, and treatments for both types needed to be offered.

In recent years, various devices enabling recording of electrocardiograms for long periods, including wearable devices such as a patch or a belt developed in Europe and North America (HealthPatch by VitalConnect, Inc., CA, United States, Spiderflash-t by LivaNova PLC, London, England, and the ePatch by Bio Telemetry, Inc., PA, United States), and subcutaneous implantable devices (Reveal XT and Reveal LINQ by Medtronic, Dublin, Ireland) have been used to detect covert AF in observational studies, with the global aim of reducing the incidence of cryptogenic stroke. As a result, several studies, such as the CRYSTAL-AF and the EMBRACE studies, reported that the detection rate for covert AF increased as the duration of electrocardiographic monitoring became longer and the detection rate within 1 year observation period was approximately 12.4% to 33.3%.15-17 A few such devices have been developed in Japan, include Duranta (ImageONE Co., Ltd.) and the long-duration electrocardiograph EV-201 (Parama Tech Co., Ltd., Fukuoka, Japan). Nevertheless, such devices, especially the wearable-type, are now available after worldwide efforts in development. However, none of them provide sufficient comfort and convenience because of the following disadvantages: limited duration of continuous monitoring; heavy weight; event recording only; requirement of lead wires; and a belt-type design.

We started a study assessing the use of the wireless patch-type electrocardiographic monitoring system Duranta for detecting
covert AF in patients in the acute phase of ESUS. This medical-use device, placed on the chest, was developed and commercialized by ImageONE Co., Ltd., Japan, initially for monitoring of patients. Until recently, covert AF has routinely been examined by 24-hours Holter ambulatory electrocardiography, the results of which become available after waiting for a couple of days. Use of Duranta enabled physician to monitor electrocardiographic data continuously and for a long duration using Microsoft Windows on remote PCs (Thirdwave Diginnos Co., Ltd., Tokyo, Japan), and this resulted in successful real-time detection of early-stage covert AF even in a patient who was initially thought to have had an artery-to-artery embolism. In our small study, 5 patients with covert AF were detected in 16 patients with cryptogenic stroke by utilizing this Duranta so far (mean observation period, 13.8±8.2 days; range, 3–31 days). Therefore, we suggested that Duranta was beneficial in the early detection of covert AF in cryptogenic stroke because our detection rate of 31.3% was never inferior to that of the previous studies as above.\textsuperscript{5–15} Furthermore, this allowed initiation of anticoagulant therapy immediately after detection of the covert AF, which greatly contributes to the prevention of recurrent cardioembolic stroke.

This study demonstrated that Duranta can detect covert AF more efficiently than 24-hours Holter ambulatory electrocardiography, providing high-quality electrocardiographic waveforms for diagnosis and further analysis, with few motion artifacts attributed to body movements. It has many advantages including small size and light weight (35g), fast and easy placement, a wireless and lead-less design resulting in no restrictions on patients’ movements, and placement without discomfort. Furthermore, it allows remote confirmation of the status of device attachment based on waveform analysis, and finally, enables real-time waveform analysis to detect covert AF. However, the device is not waterproof and requires an iPhone or an iPad to be within a certain distance for receipt of waveform data. Even with these disadvantages, Duranta, which enables continuous long-duration recording, will be beneficial.

Subcutaneous implantable electrocardiographs, such as Reveal LINQ by Medtronic, are indicated for the detection of covert AF in cryptogenic stroke. However, implanting such an invasive device in all patients with cryptogenic stroke is not feasible. Thus, in detection of covert AF, it might be plausible that a noninvasive patch-type electrocardiographic monitoring system, such as the one presented in this case, be tried first and a subcutaneous implantable electrocardiograph be used only when covert AF is not detected by a non-invasive approach. Duranta offers stable long-duration electrocardiographic monitoring and will be useful in the early detection of covert AF. Further studies would be valuable.

5. Conclusions
We are currently assessing the Duranta, a noninvasive patch-type electrocardiographic monitoring system developed in Japan, for the detection of covert AF in patients with acute embolic stroke of an unknown source. Duranta, placed on the chest, provides stable long-duration electrocardiographic monitoring, and is beneficial in the detection of covert AF in cryptogenic stroke. Further study is warranted.

Acknowledgments
None.

Figure 5. Cerebral angiography in the left common carotid artery. Cerebral angiography confirmed stenosis of the left common carotid artery (60% by the NASCET method). CCA=common carotid artery, Lt=left, NASCET=North American Symptomatic Carotid Endarterectomy Trial.
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