Role of Extended External Auto-Triggered Loop Recorder Monitoring for Atrial Fibrillation
– Validation and Utility After Catheter Ablation –

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Background: Clinical outcomes after atrial fibrillation (AF) ablation are evaluated using standard 24-h Holter monitoring, and the large spontaneous variability of AF episodes and incidence of silent AF are major limitations. Further, symptoms generally decrease after AF ablation.

Methods and Results: Newly developed extended external auto-trigger loop recorders (ELR) were used for 14-day consecutive monitoring to detect atrial tachyarrhythmia (ATa). Continuous tracings were stored for the initial 24h. Among 500 examinations after AF ablation in 342 patients, 40 ATa episodes were manually detected in 25 patients during the initial 24h. All episodes including 27 asymptomatic episodes (67.5%) were successfully identified using ELR. Recurrent ATa after AF ablation were detected in 83 patients, and a median monitoring duration of 4.0 days (IQR, 1.0–7.75 days) was required to detect the first episode of recurrence. The sensitivity of 24-h monitoring in detecting arrhythmia recurrence was 27.7% relative to the 14-day monitoring. The diagnostic yield gradually improved with longer monitoring duration regardless of the period after the ablation procedure. Longer follow-up, however, was required to obtain similar diagnostic yield >1 year after as compared to <1 year after the procedure.

Conclusions: Twenty-four-hour monitoring detected a part of the ATa recurrences after ablation procedures. Extended ELR enabled arrhythmia monitoring for longer, with higher diagnostic yield of recurrence, regardless of patient symptoms. (Circ J 2014; 78: 2637–2642)

Key Words: Atrial fibrillation; Catheter ablation; External loop recorder; Monitoring

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Arrhythmia/Electrophysiology

Original Article

Recognition and targeting of pulmonary vein (PV) triggers led to a dramatic rise in the efficacy and prominence of catheter ablation of atrial fibrillation (AF)\(^1,2\). Clinical trials assessing the catheter ablation of paroxysmal and persistent AF most often used standard 24-h electrocardiogram (ECG) monitoring to evaluate the efficacy of the intervention. Nevertheless it has been widely established that the large spontaneous day-to-day and week-to-week variability of AF episodes and the incidence of silent AF are major limitations for any conclusions based on 24-h monitoring.\(^3\) In addition, it is well known that the ratio of asymptomatic to symptomatic AF episodes significantly increases after ablation.\(^3,4\) Therefore, the use of prolonged monitoring is required for detecting recurrent atrial tachyarrhythmia (ATa) after the ablation procedure. An external loop recorder (ELR) is one of the monitoring tools to enable longer monitoring, but most available ELR have technical limitations, due to their relatively low memory capacity and lack of an auto-trigger function. The purpose of this study was to quantify the performance of the new generation ELR with large memory capacity, extended backward and forward memory, and auto-trigger functions with dedicated ATa detection capabilities in the context of post-AF ablation monitoring.\(^5\)

Methods

Subjects
This study consisted of 500 sessions of consecutive ELR monitoring for 14 consecutive days in 342 patients at Tsuchiura Kyodo Hospital between April 2012 and March 2014 (Table 1). All monitoring was done after catheter ablation of AF to evaluate clinical outcome. According to the guidelines, episodes
For the detection of asymptomatic, almost asymptomatic events, and less frequent symptomatic events, we used a newly developed extended ELR (SpiderFlash-t AFIB; Sorin, France) for 14-day consecutive monitoring. The recording consisted of continuous ECG recording for the initial 24h (same as 24-h Holter ECG), auto-trigger episodes, and patient-activated episodes for the 14 consecutive days. The SpiderFlash-t AFIB can record an ECG for up to 15min before, and 15min after detection of arrhythmia or patient activation – as often as needed, with Secure Data (SD) card technology providing a markedly expanded memory capacity (>total 25h).

SpiderFlash recorders are programmed using Hook-up2w (version 2.00), allowing the choice of several recording and pre-analysis parameters (such as the pre- and post-event recording duration, timetable for pre-defined recordings, and the type and characteristics of arrhythmias for the auto-trigger function). The auto-trigger function consists of ATa-related functions (supraventricular tachycardia and irregular RR intervals) and non-ATa-related functions (other functions). The SpiderFlash recorders are worn by the patient in a disposable bag hung around the neck. The recorders are connected to the thorax by lead wires and disposable adhesive electrodes, which the patients are trained to change daily after taking a bath. The patients had to press a button on the recorder to store the ECG tracings in case of symptoms (patient-activated events); otherwise no other manipulation was required. The patients were asked to annotate in a special diary all the symptoms occurring during the monitoring period. Analysis was done using EventScope2w (v2.00), SpiderFlash-dedicated software. The

**Table 1. Patient Characteristics**

| Characteristics | n (%) or mean±SD |
|-----------------|------------------|
| n               | 342              |
| Age (years)     | 61.7±9.4         |
| Male            | 277 (80.1)       |
| AF type         |                  |
| Paroxysmal      | 204 (59.6)       |
| Persistent      | 64 (18.7)        |
| Longstanding persistent AF | 74 (21.6) |
| Hypertension    | 166 (48.5)       |
| Left atrial diameter (mm) | 41.9±5.9 |
| LVEF (%)        | 64.7±8.7         |
| CHADS2 score    | 0.78±0.86        |

AF, atrial fibrillation; LVEF, left ventricular ejection fraction.

![Figure 1. Detection of initiation of asymptomatic atrial fibrillation (AF; red arrow) with the auto-trigger function of the external loop recorder. The initiation can be recognized on the (A) stored tracing and (B) by the change in the RR interval. PAC, premature atrial contraction; SR, sinus rhythm.](image-url)
Extended ELR Monitoring for AF

Ablation was performed according to the strategy described previously. In brief, after a single transseptal puncture, 2 long sheaths (SL0; St. Jude Medical, Minneapolis, MN, USA) were introduced into both superior PV. Pulmonary venography during ventricular pacing and contrast esophagography were used to obtain the relative locations of the PV ostia vis-a-vis the esophagus. Heparin 100 IU/kg body weight was given following the transseptal puncture, and heparinized saline was additionally infused to maintain the activated clotting time at 250–350 s. Two circular mapping catheters (Lasso; Biosense-Webster, Diamond Bar, CA, USA) were placed in the superior and inferior PV, and the left- and right-sided ipsilateral PV were circumferentially and extensively ablated, guided by a 3-D mapping system (CARTO3; Biosense-Webster). The endpoint was the achievement of bidirectional conduction block between the left atrium and PV. Radiofrequency (RF) current was delivered point-by-point with a 3.5-mm externally irrigated-tip quadripolar ablation catheter (Thermocool; Biosense-Webster) with a power of up to 35 W, target temperature ≤38°C and irrigation rate 30 ml/min. The power was limited to 20 W on the posterior wall close to the esophagus. After completing PV antrum isolation (PVAI), any adenosine triphosphate-provoked dormant conduction was eliminated using additional RF applications.

In patients with non-paroxysmal AF, substrate modification, when AF persisted after PVAI, was performed sequentially to

Figure 2. Improvement in the diagnostic yield of recurrent atrial tachyarrhythmia with a longer monitoring duration during different periods after atrial fibrillation ablation. (A) All patients; (B) <3 months; (C) 3–12 months, and (D) >12 months after ablation.
eliminate any complex fractionated atrial electrograms in both atria.\textsuperscript{3,10} The endpoint of the substrate ablation was termination of AF and restoration of sinus rhythm by ablation. If AF continued after substrate ablation, the patients underwent internal electrical cardioversion. If AF was converted to atrial tachycardia, it was mapped and ablated using 3-D activation mapping and entrainment maneuvers. When a critical isthmus of a macroreentrant circuit was identified, the lesions were deployed to achieve complete bidirectional conduction block. The cavo-tricuspid isthmus was also ablated to create bidirectional conduction block.

### Statistical Analysis

Continuous data are expressed as mean±SD for normally distributed variables or as median (25th–75th percentile) for non-normally distributed variables, and were compared using Student’s t-test or Mann-Whitney U-test, respectively. Categorical variables were compared using chi-squared test. P<0.05 indicated statistical significance.

### Results

#### Sensitivity of ELR in Detecting ATa

During the initial 24-h continuous recording, 40 ATa episodes were manually detected in 25 patients (mean age, 67±9 years; 19 male). The initiation of ATa was documented in 25 episodes (62.5%) by the ATa-related auto-trigger function (Figure 1) and in 4 episodes (10%) by patient activation. The remaining 11 episodes (27.5%) were detected by the non-AF-related auto-trigger function, but the initiation of the episodes was not documented. All 40 ATa episodes were detected using the ELR, and 27 episodes (67.5%) were asymptomatic. The positive predictive value (PPV) of the auto-triggered ELR was 5.2% per study. The sensitivity and false-negative rate of the auto-triggered ELR was 100% and 0%, respectively. The PPV of the AF detection (“irregular RR”) was 25.7% and false-positive rate was 74.3% (32.9% of noise and 41.4% of premature atrial contractions) per episode.

#### Consecutive 14-Day Auto-Triggered ELR Monitoring After AF Ablation

Recurrent ATa were detected in 83 patients (mean age, 64±10 years; 66 male), and a median monitoring duration of 4.0 days (IQR, 1.0–7.75 days) was required to detect the first episode of recurrence. For the detection of the first recurrent ATa, a median monitoring duration of 3.0 days (IQR, 1.0–7.0 days), 3.0 days (IQR, 1.5–5.5 days), and 7.0 days (IQR, 2.0–10.0 days) was required in 27, 24, and 32 patients in whom ELR was used <3 months, 3–12 months, and >12 months after ablation, respectively. The sensitivity of detecting arrhythmia recurrence with 24-h Holter monitoring was 27.7% relative to the 14-day ELR monitoring. The diagnostic yield gradually improved with longer monitoring duration. The same trend was observed for the different recording periods, but a longer monitoring duration was required to obtain a similar diagnostic yield >12 months after, than <12 months after the procedure (Figure 2).

The diagnostic yield of the 24-h Holter monitoring was 40.7% 25.0% and 18.6% <3 months, 3–12 months, and >12 months after ablation, respectively.

Among the 83 patients in whom recurrent ATa were detected using ELR, all ATa episodes were asymptomatic in 60 patients (72.3%). The clinical characteristics did not differ between the patients with and without symptoms (Table 2). The median monitoring duration required for the detection of ATa was significantly shorter in the patients with symptomatic ATa than in those without (3.0±2.8 vs. 5.0±4.1 days, P=0.046).

Among the 342 patients, 110 (32.2%) received anticoagulation therapy and 45 (13.2%) took anti-arrhythmic drugs at the last follow-up, a median of 25 months (IQR, 15–37 months) after the procedure. A stroke occurred in 1 patient (0.29%) who had recurrent silent AF and ongoing anticoagulation therapy (dabigatran) during the follow-up period. This was diagnosed by a neurologist as branch atheromatous disease.

### Discussion

To the best of our knowledge, the present study is the first to use an auto-triggered extended ELR as a long-term continuous AF monitoring device in clinical practice and to validate its diagnostic sensitivity according to manual analysis of the stored AF episodes. We found that (1) all ATa episodes were stored on the ELR regardless of symptoms; (2) 24-h Holter monitoring detected only 27.7% of the patients with recurrent ATa detected on 14-day consecutive monitoring; and (3) longer monitoring with an auto-triggered ELR improved the diagnostic yield of recurrent ATa after AF ablation, regardless

### Table 2: Clinical Characteristics and Medications in Patients With Recurrent Symptomatic ATa and Those With Recurrent Asymptomatic ATa

| Symptomatic | Asymptomatic | P-value |
|-------------|--------------|---------|
| n | 23 (27.7) | 60 (72.3) |
| Age (years) | 63.5±8.1 | 61.8±9.7 | 0.41 |
| Male | 16 (69.6) | 53 (88.3) | 0.09 |
| AF type | | | 0.33 |
| Paroxysmal | 16 (69.6) | 31 (51.7) |
| Persistent | 2 (8.7) | 7 (11.7) |
| Longstanding persistent AF | 5 (21.7) | 22 (36.7) |
| Left atrial diameter (mm) | 43.4±5.8 | 43.5±6.2 | 0.87 |
| LVEF (%) | 67.5±6.3 | 63.0±7.6 | 0.09 |
| CHADS2 score | 1.11±0.96 | 0.92±0.94 | 0.48 |
| Anticoagulation | 11 (47.8) | 28 (46.7) | 0.88 |
| Anti-arrhythmic drugs | 6 (26.1) | 10 (16.7) | 0.51 |
| Follow-up (months) | 25 (14–33) | 18 (13–29) | 0.44 |

Data given as n (%), mean±SD or median (IQR). ATa, atrial tachyarrhythmia. Other abbreviations as in Table 1.
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24-h Holter Monitoring

Several methods have been described to improve rhythm monitoring in AF patients. The 24-h Holter monitoring is most widely used for detecting arrhythmia and is the gold standard for monitoring arrhythmia recurrence after AF ablation. The advantage of this device is its high quality of consecutive ECG recording on multiple channels. The major limitation is that patients may not experience cardiac arrhythmia during the limited recording period. In general, there is considerable variability of arrhythmia episodes. It is therefore not surprising that 24-h Holter monitoring has a low diagnostic yield, because it is unlikely to capture recurrent ATa, unless the episodes are extremely frequent. Forty-eight-hour and 7-day Holter monitoring are not available in Japan, and would seem to be unsuitable considering the culture in Japan, where almost all Japanese people take a bath at least once per day.

Implantable Loop Recorder (ILR)

Although ILRs enable continuous monitoring and have a battery life of 3 years, they are invasive, expensive, and decrease quality of life. In fact, a small number of patients had later complications that were mostly related to skin erosions, especially in smaller patients. Another important limitation is the high rate of false-positive AF recordings, mainly caused by oversensings of myopotentials and noise, and the limited electrogram storage capacity that led to non-diagnostic interrogations in 38% of patients. During an initial validation study, a high sensitivity of 96.1% for detecting AF was found, while the specificity was limited by false stored AF episodes in 15% of the patients. ILR continuously classify heart rhythm by an analysis of the beat-to-beat variability of cardiac cycles on a 2-min ECG strip. Unfortunately, it can store <50 min of ECG data on 1 channel and the number of stored events is limited. To recognize false-positive AF episodes, all automatically detected episodes need to be confirmed on manual electrogram analysis, but the device is unable to preferentially retain ECG information because older episodes are deleted when new episodes are added to the device log. Prolongation of the detection period for sustained AF may be a different way to prevent episodes of AF misdetection, because false-positive AF episodes are short. Clearly, shorter AF episodes will then be unrecognized.

ELR

Most available ELR have technical limitations, due to a relatively low memory capacity and lack of auto-trigger function. A prior study showed that the auto-triggered loop recording approach provided a higher yield of diagnostic events compared to loop recording and Holter monitoring in patients with syncope. The SpiderFlash is a newly developed ELR that has the flexibility for detailed programming and a huge extended storage capacity of 2 channels of electrogram events. Although this device can monitor for a maximum of 40 consecutive days, the present study used 14-day monitoring to ensure patient compliance. The present data have demonstrated the low sensitivity of 24-h Holter monitoring, and that conclusion was universal regardless of the period after the procedure (within the blanking period: <1 year; and >1 year). In addition, a longer monitoring duration was required to obtain a similar diagnostic yield >1 year after the procedure. Accurate detection of recurrent ATa after ablation is crucial for patient management, such as anticoagulation, anti-arrhythmia treatment or repeat procedures. Therefore, an alternative monitoring system that enables rigorous long-duration monitoring is necessary.

Although extended auto-triggered ELR seems to be optimal for monitoring silent AF events, there are some limitations. Long-term compliance with this device can be challenging because of electrode and skin-related problems and waning of patient motivation in the absence of recurrent symptoms. The PPV of the ELR auto-trigger function is low, and therefore manual verification is essential. The PPV, however, is not universal and depends on the patient; that is, PPV would considerably increase if many arrhythmia events are included in the monitoring. With regard to this, we did not use this system in patients in whom recurrent AF could be easily documented with other devices (symptoms, routine 12-lead ECG, 24-h Holter monitoring, portable patient-triggered ECG monitors, etc) because 14-day recording would not provide any benefit for such patients in clinical practice. In contrast, it is notable that all ATa episodes were stored on the ELR, and no recurrence events were missed. In the present study, the duration of monitoring required for the detection of ATa was significantly shorter in patients with symptomatic ATa than in those without. It seems plausible that patients with symptomatic ATa have more frequent episodes than those without.

Due to such findings, the non-invasive and easy-to-use extended ELR with auto-trigger capability should become the first choice for the evaluation of recurrent ATa after ablation. The optimal follow-up duration and period after AF ablation should be further investigated because with more extensive monitoring, more recurrences are detected, but the workload increases and compliance diminishes. ELR seems to be a feasible device for clarifying the cause of unknown syncope, which usually has less frequent episodes and could be caused by lethal arrhythmias, but not for routine follow-up for detecting recurrent ATa after AF ablation in clinical practice.

Silent AF and Anticoagulation Therapy After AF Ablation

In the present subjects, 67.5% of recurrent ATa documented on the ELR were asymptomatic. In a prospective multicenter study 56.0% of the episodes documented on ILR were asymptomatic after AF ablation, similar to the present results. The current guidelines state that decisions regarding the continuation of systemic anticoagulation agents >2 months following ablation should be based on the patient’s risk factors for stroke and not on the presence or type of AF, and that patients who are at increased risk for stroke in whom discontinuation of systemic anticoagulation is being considered, should undergo some type of continuous ECG monitoring to screen for asymptomatic recurrences. In contrast, some non-randomized studies have shown that the risk of stroke is low in patients without recurrence after AF ablation, and this important issue is still being debated. The current study consisted of a heterogeneous patient group, but the diagnostic yield of the 24-h recordings was limited in less symptomatic patients and a longer monitoring period significantly improved the diagnostic yield of recurrent ATa. A randomized prospective study with long-term follow up should be conducted to clarify this issue, and we recommend that discontinuation of anticoagulation should be carefully considered based on the data of repeated continuous long-term monitoring to detect any silent ATa. The auto-trigger ELR might be an important tool to facilitate this important decision.

Study Limitations

The study design was not prospective. The AF burden cannot be evaluated by this system. Even such long durations of continuous monitoring may miss AF episodes, because AF often
occurs sporadically and unpredictably. The PPV of the ELR is low, and further development of software for discriminating arrhythmias would be desired.

Conclusions

Twenty-four-hour Holter monitoring identified only a part of the patients with arrhythmia recurrence after AF ablation. New-generation ELR enabled arrhythmia monitoring for a longer duration with a higher diagnostic yield of recurrence regardless of patient symptoms, increasing the likelihood of catching arrhythmia recurrence even when asymptomatic. The ELR with favorable characteristics (non-invasive, inexpensive, easy to use, reusable, and providing high-quality ECG tracings) could be viewed as the first choice for detecting recurrent arrhythmia after ablation.

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Disclosures

Conflict of Interest: None. Financial Support: None.

References

1. Haïssaguerre M, Jaïs P, Shah DC, Takahashi A, Hocini M, Quiniou G, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating from the pulmonary veins. N Engl J Med 1998; 339: 659–666.
2. Takahashi A, Iesaka Y, Takahashi Y, Kobayashi K, Takagi K, et al. Electrical connections between pulmonary veins: Implication for ostial ablation of pulmonary veins in patients with paroxysmal atrial fibrillation. Circulation 2002; 105: 2998–3003.
3. Hindricks G, Piorowikowski C, Tanner H, Kobza R, Gerds-Li JH, Carbucicchio C, et al. Perception of atrial fibrillation before and after radiofrequency catheter ablation: Relevance of asymptomatic arrhythmia recurrence. Circulation 2005; 112: 307–313.
4. Verma A, Champagne J, Sapp J, Novak P, Skanes A, et al. Discerning the incidence of symptomatic and asymptomatic episodes of atrial fibrillation before and after catheter ablation (DISCERN AF): A prospective, multicenter study. JAMA Intern Med 2013; 173: 149–156.
5. Locati ET, Vecchi AM, Vargiu S, Cattafi G, Lunati M. Role of extended external loop recorders for the diagnosis of unexplained syncope, pre-syncpe, and sustained palpitations. Europace 2014; 16: 914–922.
6. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, et al. 2012 HRS/ EHRA/ ECA expert consensus statement on catheter and surgical ablation of atrial fibrillation: Recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design: A report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. Heart Rhythm 2012; 9: 632–696.
7. Miyazaki S, Kuwahara T, Kobori A, Takahashi Y, Takei A, Sato A, et al. Long-term clinical outcome of extensive pulmonary vein isolation-based catheter ablation therapy in patients with paroxysmal and persistent atrial fibrillation. Heart 2011; 9: 668–673.
8. Uchiyama T, Miyazaki S, Taniguchi H, Komatsu Y, Kusa S, Nakamura H, et al. Six-year follow-up of catheter ablation in paroxysmal atrial fibrillation. Circ J 2013; 77: 2722–2727.
9. Miyazaki S, Taniguchi H, Komatsu Y, Uchiyama T, Kusa S, Nakamura H, et al. Sequential biatrial linear defragmentation approach for persistent atrial fibrillation. Heart Rhythm 2013; 10: 338–346.
10. Miyazaki S, Taniguchi H, Kusa S, Uchiyama T, Nakamura H, Hachiya H, et al. Impact of atrial fibrillation termination site and termination mode in catheter ablation on arrhythmia recurrence. Circ J 2013; 78: 78–84.
11. Hachiya H, Hirao K, Takahashi A, Nagata Y, Suzuki K, Maeda S, et al. Clinical implications of reconnection between the left atrium and isolated pulmonary veins provoked by adenosine triphosphate after extensive encircling pulmonary vein isolation. J Cardiovasc Electrophysiol 2007; 18: 1–7.
12. Miyazaki S, Taniguchi H, Kusa S, Uchiyama T, Hirao K, Iesaka Y. Conduction recovery after electrical isolation of superior vena cava: Prevalence and electrophysiological properties. Circ J 2013; 77: 352–358.
13. Lacunza-Ruiz FJ, Moya-Mitjans A, Martínez-Alday J, Barón-Esquivias G, Ruiz-Grancell R, Rivas-Gándara N, et al. Implantable loop recorder allows an etiologic diagnosis in one-third of patients: Results of the Spanish REVEAL Registry. Circ J 2013; 77: 2535–2541.
14. Eitel C, Husser D, Hindricks G, Fröhaut M, Hilbert S, Arya A, et al. Performance of an implantable automatic atrial fibrillation detection device: Impact of software adjustments and relevance of manual episode analysis. Europace 2011; 13: 480–485.
15. Reiffel JA, Schwarzberg R, Mierry M. Comparison of autotriggered memory loop recorders versus standard loop recorders versus 24-hour Holter monitors for arrhythmia detection. Am J Cardiol 2005; 95: 1055–1059.
16. Hunter RJ, McCready J, Diab I, Page SP, Finlay M, Richmond L, et al. Maintenance of sinus rhythm with an ablation strategy in patients with atrial fibrillation is associated with a lower risk of stroke and death. Heart 2012; 98: 48–53.