**Summary**

Esophageal injury is a rare but serious complication of atrial fibrillation (AF) ablation. To minimize esophageal injury, our persistent AF (PerAF) protocol involves complete left atrial posterior wall (LAPW) and pulmonary vein (PV) isolation (box isolation), with a centerline away from the esophagus. However, there has been a concern that extensive LA isolation might deteriorate LA function. There has been a paucity of data on LA remodeling after box isolation. Therefore, we compared LA size pre- and post-box isolation with an LAPW centerline in patients with PerAF.

Patients who underwent catheter ablation (CA) for PerAF between November 2016 and December 2018 were retrospectively evaluated.

The LAPW, including all PVs, was completely isolated in 105 consecutive patients (75 men; mean age: 68 ± 10 years) with PerAF, including 58 patients with long-standing PerAF. During a follow-up of 660 ± 332 days, 76 patients (72%) were arrhythmia-free. The LA dimension (38 ± 6 mm versus 42 ± 7 mm; \( P < 0.0001 \)) and volume index (38 ± 13 mL/m² versus 47 ± 14 mL/m²; \( P < 0.0001 \)) at 6 months post-ablation were significantly decreased in patients who maintained sinus rhythm compared to pre-ablation. In patients with recurrent AF/atrial tachycardia (AT), these parameters were also significantly decreased (\( P < 0.001 \), respectively).

Box isolation with a posterior centerline has no esophageal complications and a high clinical success rate in patients with PerAF. Reverse remodeling could be achieved even when using extensive isolation of the PV and LAPW in patients with PerAF.

(TInt Heart J Advance Publication)

**Key words:** Catheter ablation, Reducing left atrial volume, Pulmonary vein isolation

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Thermal injury of the esophagus during atrial fibrillation (AF) ablation is a serious complication. As the course of the esophagus is in close proximity to the standard pulmonary vein (PV) antral ablation posterior line, the concern of injury exists. Although recent prospective study showed a similar outcome of left atrial posterior wall (LAPW) isolation compared with PV isolation, LAPW is considered an effective method in minimizing esophageal injury and abolishing AF trigger from the LAPW in patients with persistent AF (PerAF). Briefly, the technique includes continuous lesions at the anterior ipsilateral PVs, with floor and roof lines connecting the anterior lines. As a result, the box isolation of the whole LAPW and all PVs is expected. In addition, the lengths of the lesions close to the esophagus were shorter in the floor line rather than in the vertical line along the esophagus. The main concern of the original box isolation technique is that reconnection of the entire LAPW and PV occurs in the case of a gap in the line. Thus, we modified the original box isolation technique by adding a vertical centerline away from the esophagus in the box, isolating the LAPW and PVs, and minimizing complete reconnection in the case of a gap in the line.

On the other hand, extensive LA isolation might cause the deterioration of LA function; however, there is a paucity of data on the disadvantage of LA remodeling following box isolation with centerline. Therefore, we performed a retrospective observational study to determine the effects of LA size on the posterior LA following electrical isolation by catheter ablation (CA).
Methods

Study population: A total of 123 patients who underwent CA for PerAF in Kyorin University Hospital from November 2016 to December 2018 were reviewed. These patients received pre-ablation treatments, such as anti-arrhythmic drugs and/or cardioversion. In all patients taking anti-arrhythmic drugs, the drug had been discontinued for more than 5 half-lives. No patient had received amiodarone within 2 months. If AF had been sustained for more than 2 years, cardioversion was performed to confirm the appropriate sinus node function; one patient did not receive CA to PerAF within this period because of severe sinus node dysfunction following cardioversion and did not wish to have pacemaker implant. Overall, 105 patients (75 men [71%]; mean age: 68 ± 10 years), including 58 patients (55%) with long-standing PerAF, who met the following criteria were enrolled in this study: 1) CA was performed with a NavX system (EnSite, Omaha, NE, USA), using a contact force sensing irrigation catheter (TactiCath, Abbott, Chicago, IL, USA), and 2) box isolation with a centerline was used. The exclusion criteria included the use of another three-dimensional electroanatomical mapping system, having undergone balloon-based ablation, or not having undergone CA for variable reasons, such as severe sinus node dysfunction. The study protocol was approved by the Kyorin University ethics review committee (R01-217), and written informed consent was waived because of the retrospective design.

PerAF was defined as AF episodes lasting longer than 7 days or AF that was electrically or chemically cardioverted 48 hours after symptom onset.

Catheter ablation-box isolation with centerline: All anti-arrhythmic medications were stopped for longer than 5 half-lives pre-procedurally. Oral anticoagulation medication was continued peri-procedurally. Computed tomography was used to reconstruct the LA, and transesophageal echocardiogram was used to evaluate intracardiac thrombus prior to CA in all cases. CA was performed under deep sedation with dexmedetomidine and fentanyl. An esophageal temperature monitoring probe was inserted. Catheters were positioned in the coronary sinus, His bundle recording area, and right ventricle apex via femoral venous access. Two 8- or 8.5-F long sheaths were transseptally introduced into the LA under the guidance of fluoroscopy and intracardiac echocardiography. A circular or multipolar mapping catheter was introduced through the SL1 sheath into the LA for mapping, and heparin was given to keep activated clotting time above 350 seconds. Ablation was performed with an irrigated ablation catheter (TactiCath, Abbott) using the lesion size index (LSI; LSI target values of 5 in the anterior wall and roof, and LSI target values of 4.5 at PW). Ablation was performed for a minimum duration of 15 seconds at each site or until the separation or attenuation of the local electrograms, at a maximum power of 30 W (reduced to 25 W at the PW). The esophageal temperature limit was set to 40°C during the ablation of the floor line. The isolation of PVs and the LAPW was achieved through ipsilateral circumferential antral ablation, including the LAPW with a vertical centerline to avoid esophageal injury (Figure).

If the PVs and LAPW were not isolated after the box isolation, cardioversion was performed to restore sinus rhythm. Then, if isolation was not achieved, the LA was
mapped to identify gaps during coronary sinus pacing. If there were no electrograms along the original lines at the site of earliest activation, ablation was performed adjacent to the earliest site. After the entrance and exit blocks of the LAPW and PVs were confirmed, an adenosine challenge test was performed to detect dormant conduction. If dormant conduction was documented, additional radiofrequency applications were delivered to eliminate dormant conduction. Patients with a prior history of atrial flutter underwent cavotricuspid isthmus ablation, and bidirectional block was confirmed by differential pacing. If AF was converted into atrial tachycardia (AT) or if AT was documented, additional radiofrequency applications were delivered to eliminate dormant conduction. Patients with a prior history of atrial flutter underwent cavotricuspid isthmus ablation, and bidirectional block was confirmed by differential pacing. If AF was not converted into AT, touch-up ablation was performed (10 patients; 10%).

Transthoracic echocardiography: Standard views were obtained from parasternal apical windows. Biplane left ventricular (LV) end-diastolic and end-systolic volumes were obtained from the apical four- and two-chamber views; LV ejection fraction (LVEF) was measured using the modified biplane Simpson’s method. LA volumes were measured using the biplane Simpson’s method from zoomed views in the apical four- and two-chamber views. An average of 3-5 measurements was calculated. The LA maximum volume was immediately measured prior to mitral valve opening. Pre-ablation transthoracic echocardiography (TTE) was performed within 3 months pre-procedure, and post-ablation TTE was performed after 6 months.

Follow-up and redo procedure: Patients underwent clinical review, thrice daily self-pulse check, 24-hour Holter electrocardiogram (ECG), and/or event recorder at 3, 6, and 12 months (unless patients had documented AF recurrence in the intervening period). Procedural success was defined as freedom from recurrent atrial arrhythmias lasting longer than 30 seconds after an initial 3-month blanking period. Our standard practice has been to discontinue anti-arrhythmic medications post-ablation, unless recurrent atrial arrhythmias are observed within an initial 3-month blanking period. Recurrent arrhythmias were classified as AF, AT, or both. In the case of a redo procedure, reconnection of the PVs or PW and other triggers were checked. The goal of the redo procedure was the re-isolation of the PV or LAPW and the abolition of the trigger.

Statistical analysis: Continuous variables are expressed as mean ± standard deviation with comparisons performed using either a paired Student’s t-test or Mann-Whitney U-test, where a normal distribution could not be assumed. Categorical variables are expressed as numbers and percentages and were compared using a chi-square test. Kaplan-Meier analysis was used to assess freedom from AF. All statistical analyses were performed using the SPSS software version 22.0 (SPSS, Chicago, IL, USA). A P value of less than 0.05 was considered statistically significant.

Results

Baseline characteristics: A total of 105 patients with PerAF, including 58 (55%) with long-standing PerAF (1-15 years), were evaluated using echocardiography (Table I). Although LV systolic function was preserved in the majority of patients (mean LVEF: 60.6% ± 8.0%) and the LA was dilated (LA diameter: 42 ± 6.7 mm, LA volume index: 50.7 ± 17.8 mL/m²). Moderate mitral regurgitation was found in 24% of patients. LA appendage (LAA) flow velocity was decreased (43.9 ± 19.5 cm/second), and spontaneous echo contrast was observed in 27% of patients.

Box isolation with centerline: Complete isolation of the LAPW and PVs was achieved in all patients with 3042 ± 1016 seconds of radiofrequency application. The mean procedure time was 184 ± 40 minutes. Additional cavotricuspid isthmus ablation was performed in 21 patients (20%) who had documented typical atrial flutter before or induced after the box isolation. The superior vena cava (SVC) was also isolated in 10 patients (10%) who had spontaneously premature atrial contractions or AT from the SVC with/without provocation with 5 μg of isoproterenol. In 19 patients (18%) with a low-voltage area (bipolar peak-to-peak voltage < 0.50 mV), modification of the low-voltage area was performed.

Except for contraindications, such as bronchial asthma, an adenosine provocation test was performed to check dormant conduction. In cases of dormant conduction, touch-up ablation was performed (10 patients; 10%). A summary of the procedural parameters is shown in Table II.

Complications: No esophageal fistula or ulcer was observed. In two patients who had some gastric symptom, including bloating and epigastric pain, upper gastric fiberscopes were performed without significant findings. Major
Complications requiring pericardiocentesis were observed in two patients: cerebral embolism and cardiac tamponade. The patient with cerebral embolism did not receive catheter intervention because of the thromboembolism of the distal middle cerebral artery, underwent a 2-month rehabilitation, and recovered without subsequent disability. Gastric hypomotility occurred in one patient but was resolved in 15 days with abstinence from food and observational treatment.

**Follow-up:** During the follow-up of 660 ± 332 days, AF/AT recurrence was documented in 29 patients (28%): AT in 10 patients (34%), paroxysmal AF (PAF) in 15 patients (52%), AT and PAF in 2 patients (7%), and PerAF in 2 patients (7%). When patients who remained in sinus rhythm (n = 76) were compared with those with recurrent AF/AT (n = 29), there was no significant difference in terms of patients’ characteristics, pre-ablation treatment, and AF background (Table III). In patients who maintained sinus rhythm, the LA dimension and LA volume index of 6 months after ablation were significantly decreased compared with pre-ablation (38 ± 6 mm versus 42 ± 7 mm; P < 0.0001; and 38 ± 13 mL/m² versus 47 ± 14 mL/m²; P < 0.0001; respectively); similarly, in patients with recurrent AF/AT, these parameters were significantly decreased (40 ± 6 mm versus 43 ± 6 mm; P < 0.001; and 45 ± 15 mL/m² versus 59 ± 24 mL/m²; P < 0.001; respectively), including in two patients who had recurrent PerAF, and mitral regurgitation was improved (Table IV). To exclude the impact of low-voltage modification on these measurements, the LA dimension and LA volume index were compared in patients who underwent box isolation without any additional modification, which showed the similar trend (Table V).

In addition, electrocardiographic parameters changing with time among patients with maintained sinus rhythm and recurred AF/AT were shown in Table VI. In both patients with maintained sinus rhythm and recurred AF/AT, the P wave positive/negative amplitudes in V1 of 6 months post-ablation were significant decreased compared with that of pre-ablation (90 ± 47 μV versus 67 ± 34 μV; P < 0.0001; and 79 ± 52 μV versus 60 ± 37 μV; P = 0.0356; respectively). Although the PR interval and P wave amplitude in II of 6 months post-ablation were significant decreased compared with that of pre-ablation (182 ± 38 months versus 174 ± 31 months; P = 0.0075; and 98 ± 47 μV versus 90 ± 32 μV; P = 0.0112) in patients with maintained SR, they showed no significant difference in patients with recurred AF/AT.

Of the 29 patients with recurrence, 24 underwent redo ablation at 284 days (182-1301 days). In these 24 patients, 16 had reconnection of the line (10 sites in RSPV roof, 3 sites in RSPV anterior, 2 sites RIPV anterior, 2 sites in RIPV bottom, 8 sites in RSPV roof, 8 sites in LPV-LAA ridge, and 12 sites in LIPV posterior) and 10 had extra-PV trigger (SVC in 7 patients, and LPV-LAA ridge and septum, and mitral isthmus in 1 patient, respectively), and additional ablation was performed. Of the 10 patients with recurred AT, 5 had AT related to the gap of previous ablation line, 2 had perimital AT, and 3 had localized reentrant AT in RA posterior, LPV-LAA ridge, and LA anterior wall. ATs were unmappable in two

### Table II. Procedural Parameters

| Procedure time (minutes) | 184 ± 40 |
|--------------------------|----------|
| Radiofrequency time (seconds) | 3042 ± 1016 |
| Fluoroscopy time (minutes) | 11.4 ± 5.5 |
| Box isolation with centerline | 105 (100%) |
| CTI line | 21 (20%) |
| SVC isolation | 10 (10%) |
| Mitral isthmus line | 5 (5%) |
| LA anterior line | 6 (6%) |
| Low-voltage area modification | 19 (18%) |
| Other AT/PAC ablation | 7 (7%) |
| Additional RFA to dormant conduction | 10 (11%) |
| Complications | 1 (1%) |
| Cardiac tamponade | 1 (1%) |

CTI indicates cavitricuspid isthmus; LA, left atrium; SVC, superior vena cava; AT, atrial tachycardia; PAC, premature atrial contraction; and RFA, radiofrequency ablation.

### Table III. Baseline Characteristics of Patients with Maintained Sinus Rhythm and Recurred AF/AT

|                  | SR maintained (n = 76) | Recurrent AF/AT (n = 29) | P value |
|------------------|-----------------------|--------------------------|---------|
| Age, year        | 68 ± 11               | 69 ± 8                   | 0.1897  |
| Sex (male)       | 57 (75%)              | 18 (62%)                 |         |
| AF type          |                       |                          |         |
| Per AF           | 34 (45%)              | 13 (45%)                 | 0.7911  |
| Long-standing Per AF | 42 (55%)            | 16 (55%)                 | 0.9933  |
| Height (cm)      | 166 ± 9               | 163 ± 9                  |         |
| Body weight (kg) | 68 ± 14               | 64 ± 14                  |         |
| BMI              | 24.7 ± 3.8            | 23.8 ± 3.6               |         |
| Congestive heart failure | 23 (30%)         | 11 (38%)                 | 0.4528  |
| Hypertension     | 54 (71%)              | 24 (83%)                 | 0.2198  |
| Diabetes mellitus| 15 (20%)              | 8 (28%)                  | 0.1687  |
| Prior CVA/TIA    | 5 (7%)                | 4 (14%)                  | 0.2377  |
| Coronary artery disease | 9 (12%)        | 1 (3%)                   | 0.1902  |

BMI indicates body mass index; CVA/TIA, cerebrovascular accident/transient ischemic attack; SR, sinus rhythm; AT, atrial tachycardia; and AF, atrial fibrillation.
patients. At the end of the redo procedure, no other AT/AF was induced, and at the end of the follow-up of 536 days (121-1042 days), 22 resulted in sinus rhythm maintenance. Echocardiographic evaluation was performed prior to the redo procedure.

**Discussion**

Sustained AF leads to LA enlargement, with remodeling involving atrial fibrosis. Although an acceptable outcome is achieved using box isolation, there has been a concern that the extensive isolation of LA might cause the deterioration of LA function compared with the conventional PV antrum isolation. We systematically examined LA size and function following AF ablation. A significant decrease in LA size after CA in patients with PerAF who underwent box isolation with a vertical centerline was observed. We found that there were no esophageal complications and the LA dimension and volume index at 6 months post-ablation were significantly decreased compared with that at pre-ablation (37 ± 5 mm versus 41 ± 6 mm; \( P < 0.001 \); and 42 ± 8 mL/m² versus 50 ± 16 mL/m²; \( P < 0.001 \); respectively) and that complete isolation of the LAPW and PV using box isolation with a centerline was achieved in all patients.

**Box isolation with centerline:** We performed box isolation with a centerline without increasing the risk of esophageal injury. The benefit of this approach was similar to that of the conventional extensive PV antrum isolation, and complete isolation was achieved in all patients. To check dormant conduction to the LAPW and PV, adenosine was administered, as in a previous report. Additional ablation to the dormant conduction has been reported to improve ablation outcome.10 In our series, dormant conduction was found in 10 patients: at a roof line (\( n = 7 \)), a floor line adjacent to the esophagus (\( n = 4 \)), and both floor and roof lines (\( n = 1 \)). Additional touch-up ablation abolished the dormant conduction.

**Reverse remodeling of the left atrium:** There are several previous reports on reverse remodeling following ablation, and it has been reported that the hybrid (combined endoscopic surgical epicardial and transcatheter endocardial) ablation reduced AF burden that could result in LA and LV reverse remodeling.11 In another study, the efficacy of CA in patients without PAF with severely enlarged LA and its impact on LA structural remodeling have been reported.12 In this study, all patients underwent extensive ablation of PV, LAPW, and CFAE. Therefore, the explanation of the result of this study is likely multifactorial. In comparison, our study showed that 72% of patients re-

| Table IV. Echocardiographic Parameters Changing with Time Among Patients with Maintained Sinus Rhythm and Recurred AF/AT |
|---------------------------------------------------------------|
|                  | SR maintained                | Recurrent AF/AT                  |
|                  | (Pre = 76)                  | (Post = 29)                     |
|                  | \( P \) value |                 | \( P \) value |                 |
| LA diameter 2C (mm) | 42 ± 7 | 38 ± 6 | < 0.0001 | 43 ± 6 | 40 ± 6 | 0.0183 |
| LA volume index (mL/m²) | 47 ± 14 | 38 ± 13 | < 0.0001 | 59 ± 24 | 45 ± 15 | 0.0002 |
| LA long axis dimension 4C (mm) | 61 ± 10 | 56 ± 8 | < 0.0001 | 66 ± 8 | 59 ± 10 | < 0.0001 |
| LA short axis dimension 4C (mm) | 45 ± 7 | 40 ± 7 | < 0.0001 | 48 ± 6 | 43 ± 6 | 0.0027 |
| LV EF (%) | 60 ± 8 | 61 ± 5 | 0.0731 | 63 ± 8 | 63 ± 5 | 0.6985 |
| Mitral regurgitation (≥ 2) | 19 (25%) | 4 (5%) | 0.0007 | 6 (21%) | 4 (14%) | 0.4869 |
| PFO | 3 (4%) | 2 (7%) |                 |                 |
| LAA flow velocity (cm/second) | 46 ± 20 | 37 ± 17 |                 |                 |
| Spontaneous echo contrast | 21 (28%) | 7 (24%) |                 |                 |

- C indicates chamber; SR, sinus rhythm; AT, atrial tachycardia; AF, atrial fibrillation; LA, left atrial; LAA, left atrial appendage; LV, left ventricular; LVEF, left ventricular ejection fraction; and PFO, patent foramen ovale.

| Table V. Echocardiographic Parameters Changing with Time Among Patients with Maintained Sinus Rhythm and Recurred AF/AT Excluding to Patients with Low-Voltage Area Modification |
|---------------------------------------------------------------|
|                  | SR maintained                | Recurrent AF/AT                  |
|                  | (Pre = 70)                  | (Post = 29)                     |
|                  | \( P \) value |                 | \( P \) value |                 |
| LA diameter 2C (mm) | 41 ± 7 | 37 ± 6 | < 0.0001 | 44 ± 6 | 40 ± 5 | 0.0067 |
| LA volume index (mL/m²) | 46 ± 12 | 36 ± 11 | < 0.0001 | 51 ± 9 | 40 ± 12 | 0.0001 |
| LA long axis dimension 4C (mm) | 61 ± 10 | 55 ± 8 | < 0.0001 | 65 ± 8 | 57 ± 9 | < 0.0001 |
| LA short axis dimension 4C (mm) | 44 ± 7 | 39 ± 7 | < 0.0001 | 46 ± 5 | 43 ± 6 | 0.0184 |
| LV EF (%) | 60 ± 8 | 61 ± 5 | 0.0776 | 63 ± 5 | 63 ± 3 | 0.3924 |
| Mitral regurgitation (≥ 2) | 18 (26%) | 4 (6%) | 0.0011 | 3 (19%) | 2 (13%) | 0.6264 |
| PFO | 3 (4%) | 0 (0%) |                 |                 |
| LAA flow velocity (cm/second) | 47 ± 20 | 43 ± 16 |                 |                 |
| Spontaneous echo contrast | 17 (24%) | 3 (19%) |                 |                 |

- C indicates chamber; SR, sinus rhythm; AT, atrial tachycardia; AF, atrial fibrillation; LA, left atrial; LAA, left atrial appendage; LV, left ventricular; LVEF, left ventricular ejection fraction; and PFO, patent foramen ovale.
mained recurrence-free during a relatively long-term follow-up period, although 55% of patients had long-standing PerAF. In addition, the LA dimension and LA volume index at 6 months post-ablation were significantly decreased, even in patients with recurrence. In those patients, as PerAF converted to PAF or AT, the reduced AF burden might have resulted in a reduced LA size and volume.

Finally, the electrocardiographic parameters changing with time among patients with maintained sinus rhythm and recurrent AF/AT suggested the potential electrical reverse remodeling of LA, even not only in patients with maintained sinus rhythm but also in patients with recurrent AT/AF.

**Study limitations:** This study was a single-center, retrospective study with a relatively small sample size and no control group. Our findings indicate that a larger, randomized controlled trial is warranted to determine the role of box isolation with a centerline for CA for PerAF. Although it has been reported that the recurrence of PerAF was reduced using LAPW isolation guided by electrophysiological study, we did not perform EPS prior to the PW isolation. In addition, the changes in LA size and volume were evaluated during a relatively short time period (6 months); however, significant changes in LA size and volume were revealed. In this study, LA size and mitral regurgitation level may not be enough to evaluate LA function. Functional parameters at pre-ablation during AF are not able to compare post-ablation during sinus rhythm because of the clinical subjects with PerAF, although functional parameters are important. Recurrence was judged on the basis of the symptoms, periodical ECG, Holter monitoring, event monitor as needed, and thrice daily self-pulse check. Implantable loop recorder or continuous monitoring was ideal, but not feasible, in general practice in Japan. Finally, endoscopy was not performed in all patients, but in patients who had some symptom. Although there were no patients who complained of suspected esophageal injury, there were no data regarding endoscopically detected esophageal lesions in this study.

**Conclusion**

Our findings show that, after box isolation with a centerline in patients with PerAF, including those with long-lasting PerAF, almost three-quarters of the patients demonstrated sinus rhythm maintenance. This study also yielded insight into reverse remodeling after box isolation and showed that LA size and volume were decreased after the procedure.

**Disclosures**

**Conflicts of interest:** Dr. Ueda received an endowment from Abbott, Japan. Dr. Sato received endowments from Biotronik, Japan. Dr. Togashi received an endowment from Medtronic, Japan.

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**Table VI.** Electrocardiographic Parameters Changing with Time Among Patients with Maintained Sinus Rhythm and Recurred AF/AT

|                  | SR maintained (n = 76) | Recurrent AF/AT (n = 29) |
|------------------|------------------------|--------------------------|
|                  | Pre | Post | P value | Pre | Post | P value |
| Heart rate (bpm) | 70 ± 13 | 71 ± 13 | 0.3095 | 66 ± 13 | 68 ± 10 | 0.2421 |
| PR interval (ms) | 182 ± 38 | 174 ± 31 | 0.0075 | 186 ± 37 | 176 ± 19 | 0.1238 |
| P wave amplitude in II (μV) | 98 ± 47 | 90 ± 32 | 0.0112 | 89 ± 54 | 93 ± 39 | 0.3693 |
| P wave positive amplitude in V1 (μV) | 90 ± 47 | 67 ± 34 | <0.0001 | 79 ± 52 | 60 ± 37 | 0.0356 |
| P wave negative amplitude in V1 (μV) | −69 ± 38 | −40 ± 30 | 0.0003 | −64 ± 37 | −40 ± 30 | 0.0003 |

SR indicates sinus rhythm; AT, atrial tachycardia; and AF, atrial fibrillation.
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