

Ripple Frequency Determined via a Novel Algorithm Is Associated With Atrial Fibrillation Termination and Freedom From Atrial Fibrillation



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BACKGROUND Persistent atrial fibrillation (AF) is a complex arrhythmia, and attaining freedom from AF with ablation has been challenging.

OBJECTIVES This study evaluated a novel CARTO software algorithm based on the CARTO Ripple map for AF termination and 18-month freedom from AF.

METHODS Consecutive patients who underwent first-time ablation for persistent AF were included. A high-density Ripple map was created using a Pentaray catheter. Following PVI, ablation was performed at locations with rapid Ripple activations, a protocol previously described by us. Patients were followed for 18 months to assess rhythm outcomes. A retrospective analysis was performed using the CARTO Ripple frequency software algorithm. The Ripple frequency algorithm quantifies amplitude changes in the bipolar electrogram.

RESULTS A total of 115 AF maps were analyzed from 84 patients (mean age 65.9 years, 63.1% men). The top quartile of Ripple frequency corresponded to a visual reference with 96.7% sensitivity

and 91.1% specificity. AF terminated during ablation in 88.1% of patients: pulmonary vein antrum alone (14.9%) or pulmonary vein plus nonantral sites (85.1%). The top quartile of Ripple frequency was present in nonantral areas associated with AF termination with 90.2% sensitivity and 86.5% specificity. After 14.0 ± 6.5 months and 1.2 ± 0.4 ablations, 78 (92.9%) of 84 patients were free of AF, and 79.8% were free of any atrial arrhythmia.

CONCLUSION A novel algorithm for automated analysis of CARTO Ripple frequency demonstrated good sensitivity and specificity for detecting atrial regions in persistent AF in which ablation is associated with frequent AF termination and freedom from AF during follow-up.

KEYWORDS Persistent atrial fibrillation; Ablation; Ripple map; Electroanatomic map; Ripple frequency; Atrial fibrillation ablation

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Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with a lifetime risk estimated between 21% and 33% based on retrospective analysis.¹ Medical therapy alone often fails to control symptoms adequately, and ablation is performed to improve outcomes. Pulmonary vein isolation (PVI) remains the cornerstone of ablation for paroxysmal and persistent AF.^{2,3} In paroxysmal AF, PVI with optimal contact-force radiofrequency or second-generation cryoballoon ablation results in approximately 80% 1-year freedom from AF.^{4–6} In persistent AF (defined as continuous AF beyond 7 days' duration), PVI alone has a lower success, perhaps due to non-PV drivers.^{7,8} Both

experimental^{9,10} and clinical^{11–13} findings support the hypothesis that localized drivers maintain AF. In persistent AF, ablation of localized drivers has been demonstrated in some studies to improve freedom from AF.^{12,13}

Ripple map is a software feature of the CARTO 3 electroanatomic mapping system (Biosense Webster, Irvine, CA) that graphically displays bipolar electrograms (Figure 1). This visual marker shows depolarization frequency, electrogram fractionation, and voltage. The Ripple display corresponds directly to the recorded bipolar electrogram, with no interpolation between points or other processing. Using this methodology, it is possible to visually assess all recorded electrograms within a cardiac chamber over extended time intervals. Our previous study found that high-frequency Ripple activation (HFRA) was associated with regions of spatiotemporal dispersion, and ablation of HFRA was associated with improved freedom from AF.¹⁴

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KEY FINDINGS

- The novel Ripple frequency algorithm corresponded to a visual reference with sensitivity and specificity of over 90%.
- The top quartile of Ripple frequency was present in nonantral areas associated with atrial fibrillation termination with 90.2% sensitivity and 86.5% specificity.
- Using a Ripple ablation approach, after 14.0 ± 6.5 months and 1.2 ± 0.4 ablations, 92.9% of patients were free of atrial fibrillation and 79.8% were free of any atrial arrhythmia.
- These findings support a potential association between Ripple frequency and critical areas of the atrium necessary for atrial fibrillation maintenance and possible recurrence.

This study aimed to evaluate a novel CARTO 3 software algorithm based on the CARTO Ripple map to identify high Ripple frequency locations and the relationship of these sites to AF termination and 18-month freedom from AF recurrence.

Methods

This study was a single-center retrospective evaluation of 84 consecutive patients from November 2016 to September 2021 who underwent first-time ablation for persistent AF.

Patients had documented continuous AF by electrocardiography, Holter monitor, or implanted device for >7 days and <1 year. All patients underwent AF ablation using a Ripple map–guided approach.¹⁴ Study participants were 18 years of age or older. Institutional Review Board approval was obtained, and all patients consented to research participation. The research reported in this paper adhered to the Helsinki Declaration guidelines.

Ripple Map–Guided Protocol and Mapping

To facilitate Ripple-based mapping, all patients in normal sinus rhythm (NSR) at baseline underwent AF induction with atrial burst pacing from the coronary sinus starting at 300 ms with a minimum of 200 ms. There was no predetermined burst pacing duration for the initial induction of AF. The left atrial (LA) anatomy was constructed using a Pentaray catheter (2-6-2 mm electrode spacing; Biosense Webster). Time continuous point acquisition of the entire LA chamber was performed with the Pentaray catheter using the Confidense algorithm (CARTO 3; Biosense Webster). Electroanatomic point density was set at 1 mm to diminish the variability in regional point clustering, which can be observed with alterations in Pentaray catheter movement speed. Electrode stability (a CARTO 3 Confidense feature that prevents point acquisition when electrode distance motion is above the threshold) was set at 3 mm to reduce catheter movement–induced electrogram artifact. The catheter was held stable for a minimum of 2.5 seconds. Continuous electrogram recording was performed over a minimum of 10 minutes. A minimum of 1500 bipolar electrogram points with

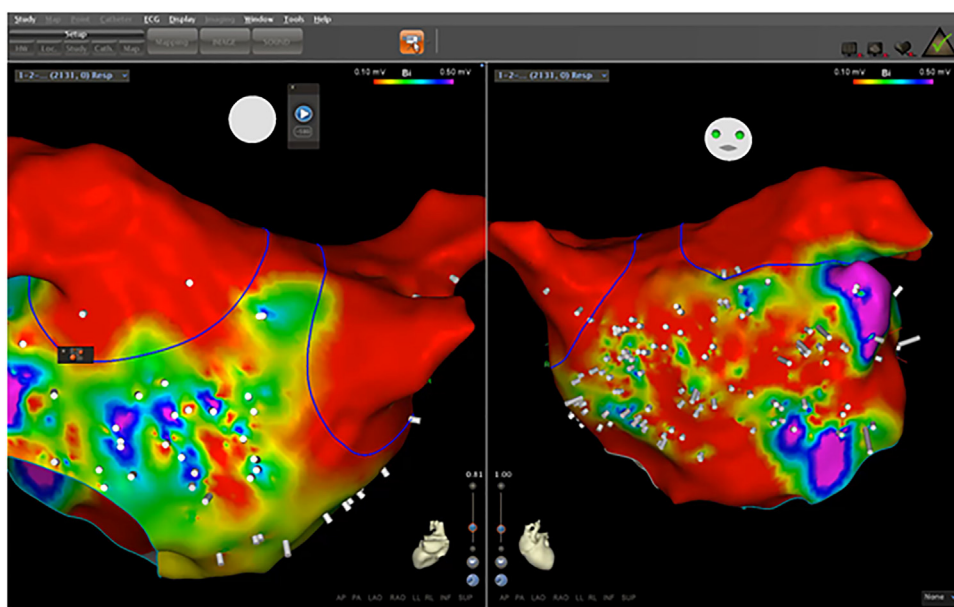


Figure 1 Example of Ripple map during sustained atrial fibrillation after pulmonary vein isolation. Color shading represents bipolar voltage displayed on the anatomic map with a range of 0.1 mV (red) to 0.5 mV (purple). White Ripple bars representing the bipolar electrograms are shown perpendicular to the map surface with the size corresponding to the bipolar voltage. A total of 2,131 points were acquired for this map with even distribution across the atrium. Some regions show no Ripple bars, indicating no depolarization at that location, rather than a lack of point acquisition. Analysis of this map demonstrated a high-frequency Ripple activation site with continuous high-frequency activation on the left atrial septum. Ablation of this location resulted in atrial fibrillation termination to normal sinus rhythm.

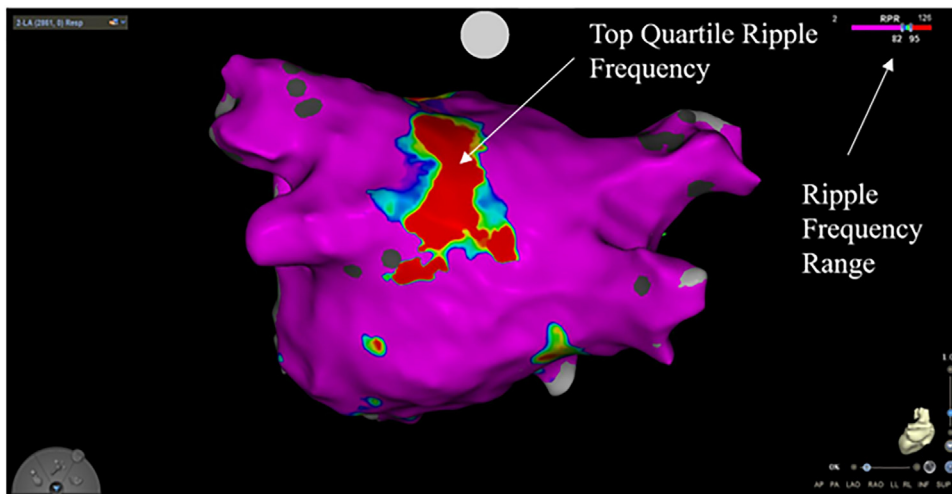


Figure 2 Example of Ripple frequency map obtained during sustained atrial fibrillation. Color shading represents the Ripple frequency. The Ripple frequency range in this example was 2 to 125 per second. The red color represents Ripple frequency more than 75% above the maximum (in this case, 95 per second). The purple color represents Ripple frequency <65% of the maximum (in this case, 82 per second). A total of 2861 points were acquired for this map with even distribution across the atrium. Analysis of this map demonstrated a large region of high Ripple frequency at the confluence of the left posterior pulmonary vein antrum and posterior wall. Ablation of this location resulted in atrial fibrillation termination to normal sinus rhythm.

equal electrogram density at all atrial locations was required to consider the map sufficient. A surface electrocardiography lead that demonstrated a dominant R-wave was used for reference annotation during point acquisition. No Confidence filters were applied (specifically, local activation time and cycle length stability).

After completing the high-density AF anatomic and point map, the Ripple map was viewed using a playback speed of 1 (this speed is an arbitrary parameter of the Ripple map program in which 1 is the slowest playback speed and 5 is the fastest). A rate of 1 corresponds to approximately 1% of real time. The lowest displayed voltage was set at 0.03 mV and the highest displayed voltage was set at 0.2 mV for viewing the Ripple map. The lower displayed voltage of 0.03 mV was necessary to correctly show regions of continuous low voltage electrograms. The upper boundary of 0.2 mV was chosen arbitrarily for map display, as the voltage was not used as a parameter to target for ablation. The Ripple window was prolonged to the maximum allowable duration of 2.5 seconds to allow for a complete display of all acquired electrograms.

HFRA was defined visually as regions of rapid and continuous Ripple activation. HFRA locations with the highest relative frequency by the visual analysis were targeted first, followed by progressively slower HFRA regions until termination. The highest frequency was explicitly defined concerning the atrium being mapped, rather than an absolute frequency. The largest anatomic regions measured on the mapping system (typically $> \sim 1.0$ -cm diameter) with HFRA were targeted for ablation first, followed by smaller areas. Isolated small segments, arbitrarily defined as < 0.5 -cm diameter, were not ablated, as these may have represented sheltered complex fractionated atrial electrograms.

Ablation Protocol

Ablation proceeded with PVI, followed by sequential ablation of the largest HFRA regions as described previously. Ablation of HFRA regions was performed in a cluster format and progressively expanded until local cycle length was observed to slow, and there was a loss of localized complex fractionated atrial electrograms and spatiotemporal dispersion. Ablation of HFRA sites was performed until AF termination occurred. Termination was determined solely by high-density electroanatomic maps with multielectrode catheters. There was no determination of rhythm etiology via surface tracings or far-field locations.

Termination as an endpoint was selected solely to test the hypothesis that HFRA sites were associated with acute AF maintenance. HFRA sites not necessary for AF termination were not subsequently ablated. If AF remained after ablation of all HFRA sites, up to 2 additional Ripple maps of the LA were performed, followed by a Ripple map of the right atrium. If AF persisted despite ablation of all HFRA regions in either chamber or if the HFRA regions were adjacent to a critical structure (eg, the AV node or sinus node), cardioversion was performed to restore NSR. Linear ablation of the LA roof was performed for induced or spontaneous roof-dependent macro-re-entrant atrial tachycardia (AT) or if extensive LA roof ablation was performed for HFRA in this location. Other linear or focal ablation was not performed unless a sustained AT was observed.

All patients underwent radiofrequency ablation using an externally irrigated, contact force sensing catheter (THERMOCOOL SMARTTOUCH and THERMOCOOL SMARTTOUCH SF; Biosense Webster). A minimum of 5 g contact was required before initiation of radiofrequency ablation. Power was fixed at 35 W and rarely increased to a

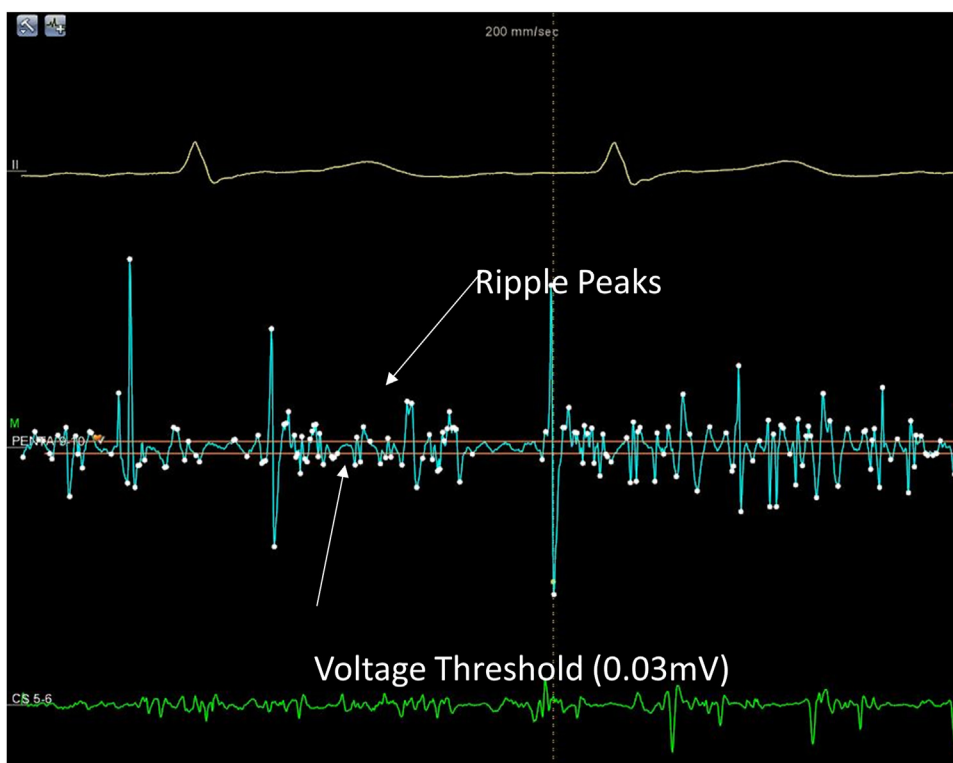


Figure 3 Example of Ripple frequency algorithm markers on an electrogram obtained during AF. The white dots represent a Ripple peak that was counted by the algorithm (noted by arrow). The Orange lines delineate the preset voltage thresholds of ± 0.03 mV from baseline 0 mV (noted by arrow). Also displayed are surface lead II, and a mid-coronary sinus electrogram.

maximum of 45 W for 60 seconds if the LA roof or lateral mitral isthmus block could not be achieved. All linear lines performed were tested for conduction block. PV entrance block was evaluated 30 minutes after initial isolation was observed, and ablation was performed if needed to re-establish antral isolation. Esophageal temperature was monitored during posterior wall ablation (level 1 temperature probe; Smiths Medical, Dublin, OH). After restoring NSR (via ablation or cardioversion), an attempt to induce AT was performed with atrial pacing for up to 5 seconds in duration above the atrial effective refractory period or a minimum of 220 ms on 2 occasions. Repeat ablation procedures for AF were performed using the same strategy.

Ripple Frequency Analysis

The maps obtained from the original study were analyzed retrospectively using the Ripple frequency algorithm. The Ripple frequency map (Figure 2) displays the calculated values as a color-coded map with a dedicated color bar representing the range of observed frequencies to simplify analysis.

The Ripple frequency algorithm is an automated method for quantifying the number of directional changes in the Ripple-based voltage over time (dV/dT) above a preset amplitude threshold during the complete 2.5-second interval of the acquired point (Figure 3). The algorithm marks only positive or negative peaks when the signal is above the preset positive or negative threshold (typically 0.03 mV). The total peaks count for all algorithm-measured changes of the

acquired electrogram was divided by 2.5 seconds to generate the Ripple frequency (defined as the Ripple peak count per second). The sites with the highest quartile of Ripple frequency within the LA, defined as the fastest 25% of all frequency measurements, were specified as the Ripple frequency regions of interest for further analysis.

To determine the sensitivity and specificity of the Ripple frequency algorithm, the LA was divided into 8 segments (PVs, posterior, inferior, septal, roof, anterior, base of the LA appendage, and lateral). Visual HFRA was utilized as the reference, and the highest quartile of the Ripple frequency map (75% or greater [ie, top 25%]) was then compared with the locations of visual HFRA. If 50% or more of the area identified with Ripple frequency overlapped with the visual HFRA reference, the site was determined to have correctly corresponded to the reference. The reference visual HFRA and Ripple frequency analysis were performed isolated from each other, and simultaneous side-by-side analysis was not performed. Ganglionated plexi (GP) were prespecified based on anatomic location and included the following: anterior right GP, inferior right GP, inferior left GP, superior right GP, and Marshall tract GP.¹⁵ In the event that AF terminated with PV isolation, the Ripple frequency data were analyzed. However, these patients were not included in further analysis of Ripple frequency performance for identifying non-PV regions of interest.

Monitoring for rhythm outcomes was performed by clinical symptom assessment, routine electrocardiograms, and

Table 1 Characteristics of the patients at baseline (N = 84)

| Characteristic | Ripple map strategy |
|--|---------------------|
| Age, y | 65.9 ± 10.3 |
| Male | 53 (63.1) |
| Structural heart disease* | 11 (13.1) |
| Left atrial diameter, mm | 44 ± 6 |
| Ejection fraction, % | 54.3 ± 9.7 |
| Duration from first AF diagnosis, mo | 37.4 ± 58.8 |
| Duration uninterrupted AF before RFA, mo | 5.1 ± 6.3 |
| Medical history | |
| Diabetes | 10 (11.9) |
| Hypertension | 43 (51.2) |
| Stroke or transient ischemic attack | 8 (9.5) |
| Vascular disease | 16 (19.0) |
| CHA ₂ DS ₂ -VASc score | 2.4 ± 1.6 |
| Pacemaker or ICD | 8 (9.5) |
| Preablation medications | |
| BB or CCB | 74 (88.1) |
| Class Ic or III AAD | 73 (86.9) |
| Class Ic AAD | 23 (27.4) |
| Class III AAD | 63 (75.0) |
| More than 1 AAD | 11 (13.1) |
| DOAC or warfarin | 73 (86.9) |

Values are mean ± SD or n (%).

AAAD = antiarrhythmic drug; AF = atrial fibrillation; BB = beta-blocker; CCB = calcium-channel blocker; CHA₂DS₂-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65-74 years, sex category; DOAC = direct oral anticoagulation; ICD = implantable cardioverter-defibrillator; RFA = radiofrequency ablation.

*Congestive heart failure, constrictive pericarditis, amyloid cardiomyopathy, valvular cardiac surgery, hypertrophic cardiomyopathy.

when available, implanted device interrogation and ambulatory rhythm monitoring. Systemic, scheduled ambulatory rhythm monitoring was not performed. Rhythm outcomes included any atrial arrhythmia on or off antiarrhythmic drug (AAD), as well as AF on or off AAD and AT on or off AAD.

Continuous variables were compared using the Student's *t* test with a statistical significance preset at .05.

Results

Patients

Eighty-four consecutive patients underwent a first-time ablation for persistent AF using a Ripple map-guided approach. Baseline demographics are listed in Table 1. In these patients, the mean duration of uninterrupted AF before ablation was 5.1 ± 6.3 months. Structural heart disease was present in 13.1%. As determined by long-axis echocardiography, the mean LA diameter was 44 mm. LA enlargement (>40 mm) was present in 65.5% of patients. The mean CHA₂DS₂-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65-74 years, sex category) risk score was 2.4 ± 1.6. In these patients, 73 (86.9%) of 84 had failed either a class Ic or class III antiarrhythmic medication, and 13.1% had failed more

Table 2 Ablation procedure results (N = 84)

| Variable | Ripple map strategy |
|---|---------------------|
| AF termination via RFA | 74 (88.1) |
| Mode of termination | |
| NSR | 9 (12.2) |
| AFL | 30 (40.5) |
| Typical/CTI-dependent AFL | 8 (11.0) |
| Focal AT | 15 (20.3) |
| MAT | 20 (27.0) |
| NSR via ablation | 64 (76.2) |
| NSR via cardioversion | 20 (23.8) |
| RFA time, min | |
| Total (all locations) | 56.9 ± 18.4 |
| Non-PV locations (including AT/AFL) | 19.7 ± 15.7 |
| Initial mean LA pressure, mm Hg | 14.9 ± 4.7 |
| CARTO atrial volume, mL | 167.5 ± 44.1 |
| RF Sites associated with AF termination | |
| PV antral isolation alone | 11 (14.9) |
| Septal LA | 47 (63.5) |
| LA roof | 32 (43.2) |
| Inferior LA | 29 (39.2) |
| Base of LAA | 21 (28.4) |
| Lateral LA | 21 (28.4) |
| Posterior LA | 19 (25.7) |
| Anterior LA | 18 (24.3) |
| Procedure duration, h | 2.8 ± 0.7 |
| Fluoroscopy time, min | 1.2 ± 1.8 |
| AF pace induced at procedure onset | 16 (19.0) |

Values are mean ± SD or n (%).

AF = atrial fibrillation; AFL = atrial flutter; AT = atrial tachycardia; CTI = cavotricuspid isthmus; LA = left atrium/atrial; LAA = left atrial appendage; MAT = multifocal atrial tachycardia; NSR = normal sinus rhythm; PV = pulmonary vein; RFA = radiofrequency ablation.

than 1 antiarrhythmic medication. Anticoagulation with either warfarin or a direct oral anticoagulant was administered before ablation in 73 (86.9%) of 84 patients.

Acute Procedure Characteristics and Outcomes

The mean procedure duration was 2.9 hours. At procedure onset, elevated mean LA pressure (>12 mm Hg) was present in 64.3% of patients (Table 2). AF was present at the procedure start in 44 (81.0%) of 54. Sustained AF was pacing-induced in 10 (19.0%) of 54 patients.

PVI was performed in all patients. Acute AF termination during the index ablation procedure was observed in 74 (88.1%) of 84 patients (14.9% with PVI alone and 75.1% with PVI plus nonantral ablation): 12.2% terminated to NSR, 29.7% to atypical, non-cavotricuspid isthmus-dependent atrial flutter, 10.8% to typical cavotricuspid isthmus-dependent atrial flutter, 20.3% to focal AT, and 24.5% to multifocal AT. In those with AF termination, a mean of 2.8 ± 2.1 non-PV HFRA sites were ablated (Figure 4). Ablation of observed ATs was performed until sinus rhythm was restored in 64 (76.2%) of 84 patients. Cardioversion was performed to restore NSR for multifocal atrial tachycardia in 11 (13.1%) patients and AF in 9 (10.7%) patients. All other ATs were ablated until NSR was observed. Mapping and ablation were performed in the right atrium in 8 (9.5%) patients when AF did not terminate with LA ablation alone.

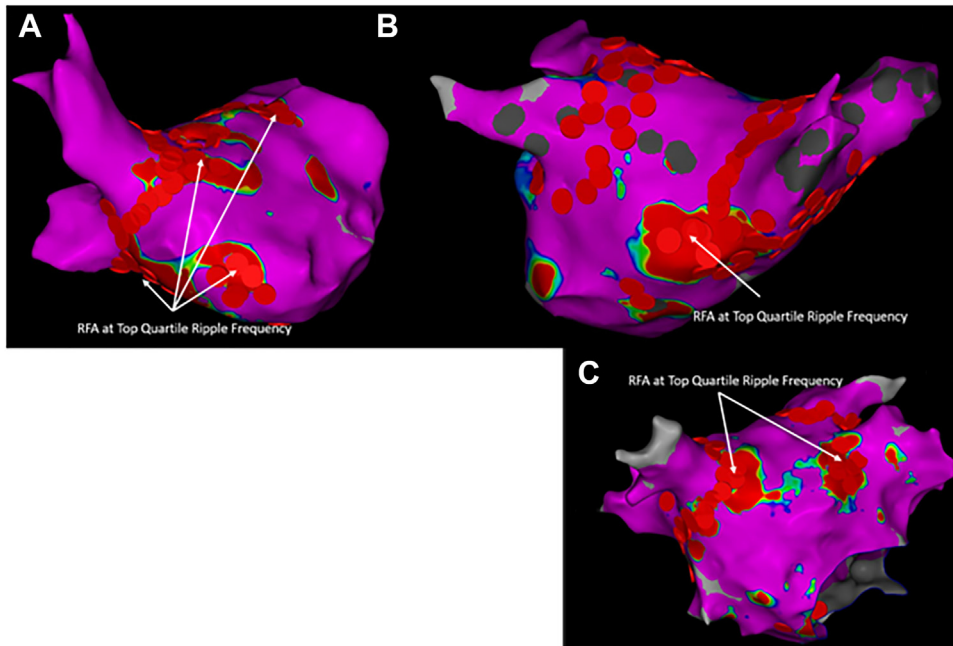


Figure 4 Examples of radiofrequency ablation lesion distributions. Ripple frequency maps in 3 patients undergoing first-time ablation for persistent atrial fibrillation (AF). Displayed are the Ripple frequency maps with the top quartile in red and the ablation lesions performed during the cases (red dot markers). **A:** The top quartile of Ripple frequency was observed at the left atrial septum inferior and superior as well as at the base of the left atrial appendage. Ablation at these sites resulted in AF termination to right atrial flutter. **B:** The top quartile of Ripple frequency was observed inferior left atrium adjacent to the right inferior pulmonary vein antrum. Ablation at this site resulted in AF termination to normal sinus rhythm. **C:** The top quartile of Ripple frequency was observed at the posterior superior septum adjacent to the right superior pulmonary vein antrum as well as the base of the left atrial appendage. Ablation at these sites resulted in AF organization to mitral isthmus–dependent flutter.

There were no major procedural complications (transient ischemic attack, cerebrovascular accident, pericardial effusion, atriopharyngeal fistula) within 30 days of the initial ablation.

Ripple Frequency Results

A total of 115 maps with 348,748 points from 84 patients were analyzed using the Ripple frequency algorithm. The mean point density was 14.3 ± 9.9 per cm^2 (Table 3). The mean number of maps per patient was 1.4 ± 0.6 . The highest quartile of Ripple frequency was present in non-PV sites necessary for AF termination with a 90.2% sensitivity and 86.5% specificity. The most common non-PV sites associated with AF termination were the LA septum 63.5%, LA roof region 43.2%, and inferior LA 39.2%.

The maximum Ripple frequency observed was 115.4 ± 25.2 (range, 58–191) per second. The highest quartile of Ripple frequency started at 81.8 (range, 31.5–111.8) per second. The Ripple frequency decreased significantly after the ablation of regions observed on the initial map compared with subsequent maps (115.4 ± 25.2 per second vs 100.9 ± 26.0 per second; $P = .006$).

The mean number of atrial regions per map containing the highest quartile of Ripple frequency was 4.6. The highest quartile of Ripple frequency comprised a surface area of 11.6 ± 10.2 (range, 0.6–38.1) cm^2 , encompassing $5.6 \pm 5.1\%$ of the total atrial surface area with a range of 0.3% to 20.1%.

The most common region demonstrating Ripple frequency in the highest quartile in 90.4% of patients was the left side of the interatrial septum. The inferior LA (66.7%), PV antrum (65.5%), and the base of the LA appendage (61.9%) were the next most common. GPs were common anatomic locations to observe high Ripple frequency. The highest quartile of Ripple frequency was noted in 83 (98.8%) of 84 patients at 1 of the 5 GP locations. In addition, the GPs comprised 44.9% of the total locations.

The highest quartile of Ripple frequency sites exhibited a 96.7% sensitivity and 91.1% specificity for correctly identifying atrial regions identified with visual HFRA analysis.

Efficacy Outcomes

After a mean follow-up of 14.0 ± 6.5 months, as documented by symptoms, electrocardiogram, Holter monitor, or device interrogation, 78 (92.9%) of 84 patients were free of AF, 70 (83.3%) of 84 patients were free of either focal AT or atrial flutter, and 67 (79.8%) of 84 patients were free of any sustained atrial arrhythmia (Table 4). A mean number of 1.2 ablation procedures were performed per patient. The second ablation was performed after 8.4 ± 4.7 months following the first procedure. Cardioversion was required for sustained AF or AT within 90 days of the index ablation in 17.6% of patients. At the last follow-up, 30.9% of patients remained on antiarrhythmic therapy.

Table 3 Ripple frequency results (N = 84)

| Result | Ripple frequency strategy |
|---|---------------------------|
| Number of acquired points analyzed (all patients) | 348,748 |
| Acquired point density, points per cm ² | 14.3 ± 9.9 |
| AF Ripple frequency maps performed | 1.4 ± 0.6 |
| 1 | 54 (64.3) |
| 2 or 3 | 30 (35.7) |
| Maximum Ripple frequency, map #1 | 115.4 ± 25.2 |
| Maximum Ripple frequency, map #2/#3 | 100.9 ± 26.0 |
| Ripple frequency range | 0–191 |
| Highest-quartile Ripple frequency range | 81.8 ± 22.4–115.4 ± 25.2 |
| Number of atrial regions highest-quartile Ripple frequency | 4.6 ± 1.8 |
| Location of LA regions with highest-quartile Ripple frequency (n = 82 maps) | |
| Septal | 76 (90.4) |
| Inferior | 56 (66.7) |
| PV antrum | 55 (65.5) |
| Anterior base of LAA | 52 (61.9) |
| Anterior | 45 (53.6) |
| Roof | 43 (51.2) |
| Posterior | 40 (47.6) |
| Lateral | 32 (38.1) |

Values are n, mean ± SD, or n (%).

AF = atrial fibrillation; LA = left atrial; LAA = left atrial appendage; PV = pulmonary vein;

Discussion

Main Findings

This study evaluated a novel algorithm designed to quantify Ripple map–based changes in the bipolar electrogram. The key findings were the following: (1) the highest quartile of Ripple frequency was present in non-PV sites associated with AF termination with a 90.2% sensitivity and 86.5% specificity; (2) the Ripple frequency algorithm had high sensitivity and specificity for identifying reference HFRA locations in persistent AF patients; and (3) over an 18-month follow-up period, ablation of HFRA sites was associated with a 92.9% freedom from AF and a 79.8% freedom from AT or AF after a median of 1.2 ablation procedures. These findings support a potential association between Ripple frequency and critical areas of the atrium necessary for AF maintenance and possible recurrence. The mean atrial surface area comprising the highest Ripple frequency was a modest 5%, indicating that extensive ablation may not be necessary to adequately eliminate regions of the atrium important for AF maintenance and recurrence risk.

Other Observations

In prior studies, a Ripple map has been utilized to identify repetitive focal and re-entrant activation during sustained AF¹⁶ and abnormal atrial potentials during sinus rhythm in nonparoxysmal AF.¹⁷ In these studies, ablation of identified regions

Table 4 Follow-up observations (N = 84)

| Variable | Ripple Map Strategy |
|---|---------------------|
| Follow-up duration, d | 406 ± 141 |
| Freedom from documented arrhythmia | |
| AF | 78 (92.9) |
| AT/AFL | 70 (83.3) |
| Any atrial arrhythmia | 67 (79.8) |
| Additional ablation performed for AF or AT/AFL | 15 (22.0) |
| Number of ablations performed per patient | 1.2 ± 0.4 |
| Cardioversion for AF or AT/AFL within 90 days of index ablation | 15 (17.9) |
| AAD at last follow-up | 18 (26.4) |
| Holter performed or implanted device present | 26 (31.0) |

Values are mean ± SD or n (%). Freedom from any atrial arrhythmia, as well as AF and AT/AFL were determined on or off AADs.

AAD = antiarrhythmic drug; AF = atrial fibrillation; AFL = atrial flutter; AT = atrial tachycardia.

of interest on the Ripple map resulted in improved termination of AF and freedom from AF during the 12 months of follow-up. These studies differ from our current study regarding the Ripple frequency algorithm in 2 respects. The Ripple frequency algorithm is quantitative, in contrast to the visual observations used to identify repetitive wavefronts or abnormal atrial potentials. Secondly, Ripple frequency does not perform wavefront analysis; instead, it measures predefined electrogram characteristics.

High-density, precise mapping of Ripple frequency in patients with persistent AF may provide insights into regions of the atrium necessary for supporting AF. We found in this study that multiple locations (eg, LA septum, LA inferior) more often contained high Ripple frequency than the PV antrum. This supports prior observations of infrequent AF termination with PVI alone.⁶ The atrial characteristics observed with Ripple frequency had wide variability between patients, with peak Ripple frequency ranging from 58 to 191 per second, suggesting significant interpatient differences in the pathophysiology and underlying substrate of persistent AF. In addition, GPs often demonstrated high Ripple frequency, with 98.8% of patients exhibiting at least 1 GP in the top quartile of Ripple frequency. In our study, however, non-GP locations associated with AF maintenance were more common than GP locations and may help explain the mixed outcomes with GP ablation alone.¹⁸

The Ripple frequency algorithm provides a relatively simple, quantitative assessment of regions of interest during AF, spatially located efficiently on a 3-dimensional electroanatomic CARTO 3 map.

Limitations

Several limitations restrict the scope of this study's findings. This was a single-center retrospective study, and multicenter evaluation is needed to improve the determination of the algorithm's efficacy. In addition, the algorithm's calculated sensitivity and specificity were based on a reference visual

Ripple analysis. Visual estimation lacks the quantitative precision necessary for a true reference and has the potential for observer bias. Systematic outpatient telemetry monitoring was not performed, so the arrhythmia recurrence may have been underestimated. The right atrium was not routinely mapped at baseline, and therefore this study may underestimate the importance of high-frequency sites in this chamber. We also acknowledge that the stability of Ripple activation sites of interest prior to PVI has not been established, and may in at least a subset of patients, result in inaccurate localization. It is reasonable that future studies using this technique may benefit from Ripple mapping after PVI is complete. Finally, this work's retrospective nature does not allow conclusions to be drawn regarding the outcomes of using the Ripple frequency algorithm prospectively to determine ablation targets.

Conclusion

This study supports the potential that a novel automated analysis of Ripple frequency may provide a complementary method to existing techniques such as spatiotemporal dispersion analysis to identify regions of interest in persistent AF.

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Patient Consent: All patients consented to research participation.

Ethics Statement: Institutional Review Board approval was obtained, and the research reported in this paper adhered to the Helsinki Declaration guidelines.

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