Specific electrogram characteristics impact substrate ablation target area in patients with scar-related ventricular tachycardia—insights from automated ultrahigh-density mapping

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Abstract

Introduction: Substrate-based catheter ablation approaches to ventricular tachycardia (VT) focus on low-voltage areas and abnormal electrograms. However, specific electrogram characteristics in sinus rhythm are not clearly defined and can be subject to variable interpretation. We analyzed the potential ablation target size using automatic abnormal electrogram detection and studied findings during substrate mapping in the VT isthmus area.
Methods and Results: Electrogram characteristics in 61 patients undergoing scar-related VT ablation using ultrahigh-density 3D-mapping with a 64-electrode mini-basket catheter were analyzed retrospectively. Forty-four complete substrate maps with a mean number of 10319 ± 889 points were acquired. Fractionated potentials detected by automated annotation and manual review were present in 43 ± 21% of the entire low-voltage area (<1.0 mV), highly fractionated potentials in 7 ± 8%, late potentials in 13 ± 15%, fractionated late potentials in 7 ± 9% and isolated late potentials in 2 ± 4%, respectively. Highly fractionated potentials (>10 ± 1 fractionations) were found in all isthmus areas of identified VT during substrate mapping, while isolated late potentials were distant from the critical isthmus area in 29%.

Conclusion: The ablation target area varies enormously in size, depending on the definition of abnormal electrograms. Clear linking of abnormal electrograms with critical VT isthmus areas during substrate mapping remains difficult due to a lack of specificity rather than sensitivity. However, highly fractionated, low-voltage electrograms were found to be present in all critical VT isthmus sites.

**KEYWORDS**
ablation, abnormal electrograms, low-voltage, mapping, substrate characterization, ventricular tachycardia

1 | INTRODUCTION

Scar-related ventricular tachycardia (VT) is increasingly treated with catheter ablation as recurring VT and consecutive implanted cardioverter-defibrillator-therapies are associated with high morbidity and mortality.

Substrate-based ablation approaches, targeting low-voltage areas and abnormal electrograms are an established technique, since mapping and ablation during VT is often hemodynamically not tolerated. However, specific electrogram characteristics during substrate mapping have not been linked precisely to the critical isthmus area of VT, which is only a small part of the entire scar. Whenever VT mapping (activation or entrainment) and direct characterization of the circuit is not possible, ablation covering the entire substrate appears to achieve better outcomes than incomplete substrate modification. The scar area after myocardial infarction can be large, leading to extensive ablation. Furthermore subtle, non-transmural myocardial scars might not be delineated using 3.5 mm tip catheters only. Still, modifying the substrate without eliminating it completely may promote arrhythmia recurrences.

Therefore, beyond the anatomical low-voltage substrate, thorough analysis of the functional substrate in regards of activation pattern and timing in sinus rhythm (SR) is of high importance. Of particular interest in this context are fractionated and late electrograms (late potentials [LP]). However, definitions are not homogeneous and as for low-voltage areas, not all abnormal electrograms are associated with the critical reentry isthmus as they can be found over wide areas.

With advances in catheter technology, especially decrease in electrode size, spacing and electrode design, novel insights into VT mechanisms and arrhythmia substrate have been described. Multi-electrode mapping of abnormal electrograms has been found to increase the sensitivity with which areas of scar are identified. Small and closely spaced electrodes allow identification of distinct diastolic activity (including diastolic pathways) that may not be seen with standard linear catheters. Moreover, automatic detection of abnormal electrograms may help overcoming subjective judgment and accelerate revision of ultrahigh-density 3D-maps with a huge number of acquired points. Whether and how this might enable a further in-depth understanding of the arrhythmia’s mechanism remains to be demonstrated.

In the present study, we aimed to investigate the size of potential ablation target areas depending on automatic detection of abnormal electrograms and furthermore analyzed the specific electrograms at the critical VT isthmus site using ultrahigh-density 3D-mapping.

2 | METHODS

2.1 | Study design

Postprocedural analysis of 65 consecutive procedures in 61 patients who were referred to our tertiary-care center for radiofrequency catheter ablation of scar-related VT was performed (see Figure 1). Data collection and analysis were performed under a protocol approved by the institutional ethics committee. All patients gave written informed consent.
2.2 | Electrophysiological evaluation and instrumentation

All patients underwent the procedure in the fasting state under conscious sedation. Hyperthyroidism or other reversible causes of VT were excluded before the procedure. Detailed procedure methods have been described before.3 Briefly, the catheter setting consisted of a 6 French (F) quadripolar diagnostic catheter, placed in the right ventricular (RV) apex to induce VT by programmed stimulation with a fixed protocol. The induced VT was defined as the clinical VT, when cycle length (CL) and morphology matched previous recordings (CL within 20 ms; 12-lead-ECG and/or device recordings). A catheter in the coronary sinus (CS) served as reference for the 3D-electroanatomical mapping system in most cases. Unfractionated Heparin was administered intravenously to maintain an activated clotting time greater than 300 s during the procedure.

2.3 | Ultrahigh-density 3D-mapping with multisize electrode catheters

Ultrahigh-density 3D-mapping was performed using the Rhythmia (Boston Scientific) mapping system as previously described.3 An expandable, 64-polar mini-basket catheter (Orion; Boston Scientific) comprising eight splines with eight electrodes each (electrode spacing 2.5 mm, electrode surface area 0.4 mm²) and an open-irrigated 3.5 mm tip mapping and ablation catheter (INTELLANAV OI/IntellaNAV MIFI OI; Boston Scientific) were introduced into the left ventricle (LV).7 Access to the LV was gained either by transseptal access after a single transseptal puncture using a fixed curve long sheath (SL0, 8.5F, St. Jude Medical; for ablation catheter) and a long steerable sheath (Agilis large curve, 8.5F, St. Jude Medical, for mini-basket catheter) or by retrograde aortic access (Terumo 8F).

The basket catheter was used to create an ultrahigh-density electroanatomical map of the LV or RV for substrate and, if possible, activation mapping during VT. Electrogram annotation was performed automatically by the mapping system as previously described.3
Substrate maps were considered complete when the entire chamber anatomy was reconstructed with the best achievable electrode-tissue contact and scar borders were clearly defined. Activation maps were considered complete when ≥90% of the VT CL was mapped. Maps were acquired with the basket catheter and subsequently completed with the single-tip ablation catheter in areas less accessible.

In line with previous studies for scar demarcation a bipolar endocardial voltage of 0.1/1 mV (dense scar <0.1 mV, border zone 0.1–1.0 mV, healthy tissue greater than 1.0 mV) with individual adaptation was chosen. All voltage maps were generated during SR, CS, or ventricular pacing. The extent of areas with fractionated and late electrograms, LV- and low-voltage area were measured using the integrated measuring tool in all patients with complete substrate maps after the procedure. Two areas were considered continuous if the distance between was less than 0.5 cm. Slow conduction was defined by crowding in the isochronal map.

Whenever VT was inducible and hemodynamically tolerated, activation mapping was performed. The critical isthmus was defined as region between conduction barriers and between inward curvature (entrance) and outward curvature (exit of the common pathway). Hemodynamic instability was defined as mean arterial blood pressure below 50 mmHg. If activation mapping was possible and the reentrant circuit was completely identified, detailed review of electrograms during sinus or paced rhythm in the critical VT isthmus zone was performed.

![Automated annotation of late potentials. Bipolar left ventricular voltage map (B) and corresponding electrogram (A) within two windows-of-interest (1,2). After adjusting the second (green) window-of-interest (2) to after the QRS, (B) only areas with electrograms in this time frame are displayed highlighted.](image)

**TABLE 1** Baseline descriptive statistics

| Variable                                      | Total cohort (n = 61) |
|-----------------------------------------------|----------------------|
| Age, years                                    | 64.9 ± 12.7          |
| Male sex, n (%)                               | 57 (93.4)            |
| Body mass index, kg/m²                        | 28.3 ± 3.9           |
| Cardiomyopathy type, n (%)                    |                      |
| Ischemic                                       | 37 (60.7)            |
| Nonischemic                                    | 24 (39.3)            |
| Arterial hypertension, n (%)                  | 43 (70.5)            |
| Diabetes, n (%)                               | 13 (21.3)            |
| Chronic kidney disease, n (%)                 | 22 (36.1)            |
| Atrial fibrillation, n (%)                    | 26 (42.6)            |
| Oral anticoagulation, n (%)                   | 32 (52.5)            |
| Left ventricular ejection fraction, (%)       | 36 ± 12              |
| Syncope, n (%)                                | 13 (21.3)            |
| Implanted cardioverter-defibrillator, n (%)   | 57 (93.4)            |

Note: Unless noted, values are mean ± standard deviation or n (percent).
In hemodynamically not tolerated VT we aimed to map repeatedly for short lasting episodes. Additional entrainment or pace mapping was performed at the operator’s discretion.\textsuperscript{11}

### 2.4 Analysis of abnormal electrograms

Electrogram review was performed by two independent electrophysiologists. Minimum characteristics for electrogram classification are shown in Figure 2.

#### TABLE 2 Low-voltage and abnormal electrogram areas

| Distribution of abnormal electrograms | % of Total mapped LV area | % of Low-voltage (<1.0 mV) |
|---------------------------------------|---------------------------|---------------------------|
| Low-voltage < 1.0 mV                   | 52 ± 24                   | 100                       |
| Low-voltage < 0.1 mV                   | 9 ± 10                    | 16 ± 17                   |
| Fractionated potentials                | 29 ± 18                   | 43 ± 21                   |
| Highly fractionated potentials         | 4 ± 4                     | 7 ± 8                     |
| Late potentials                        | 7 ± 8                     | 13 ± 15                   |
| Fractionated late potentials           | 5 ± 6                     | 7 ± 9                     |
| Isolated late potentials               | 0.8 ± 1.3                 | 1.6 ± 3.6                 |

| Number of areas per patient           | Mean number of areas per patient | Association of areas to VT isthmus site |
|---------------------------------------|----------------------------------|----------------------------------------|
| Fractionated potentials               | 3.1 ± 2.2                        | 16/48                                  |
| Highly fractionated potentials        | 2.3 ± 2.1                        | 16/38                                  |
| Late potentials                        | 1.6 ± 1.5                        | 10/29                                  |
| Fractionated late potentials          | 1.6 ± 1.5                        | 7/26                                   |
| Isolated late potentials              | 0.7 ± 1.1                        | 6/14                                   |

| Comparison of patients with ischemic and nonischemic cardiomyopathy | Patients with ICM % of total mapped LV area | Patients with NICM % of total mapped LV area | p Value |
|---------------------------------------------------------------------|-----------------------------------------------|-----------------------------------------------|---------|
| Low-voltage < 1.0 mV                                               | 57 ± 23                                       | 44 ± 26                                       | .121    |
| Low-voltage < 0.1 mV                                               | 11 ± 11                                       | 5 ± 6                                         | .063    |
| Fractionated potentials                                            | 33 ± 16                                       | 21 ± 19                                       | .038    |
| Highly fractionated potentials                                     | 5 ± 4                                         | 0.9 ± 1.3                                     | .001    |
| Late potentials                                                     | 7 ± 8                                         | 6 ± 7                                         | .706    |
| Fractionated late potentials                                       | 6 ± 7                                         | 2.4 ± 2.8                                     | .101    |
| Isolated late potentials                                           | 0.7 ± 1.2                                     | 0.9 ± 1.5                                     | .696    |

Note: Values are mean ± standard deviation or n/n total. p Value less than .05 is considered significant.

Abbreviations: ICM, indicates ischemic cardiomyopathy; LV, left ventricle; mV, millivolt; NICM, nonischemic cardiomyopathy; VT, ventricular tachycardia.
specificity. FrP included also potentials with higher degree of fractionation. Areas with LP were identified by adjusting the second window of interest to after the QRS offset (Figure 3) and confirmed by manual revision. The definition of LP included either all potentials recorded solely or partially after the QRS offset (LP), continuous fragmented (≥5 fractionations) activity bridging from within the QRS to beyond its offset (fractionated LP, frLP), or isolated potentials after the QRS offset separated by a minimal 20 ms interval from activation during QRS (isolated LP, iLP).\(^6\)\(^{12-14}\)

2.5 | Ventricular tachycardia ablation

VT ablation strategy has been described before.\(^3\) In brief, we aimed to achieve the combined procedural endpoint of VT non-inducibility and complete substrate modification. Radiofrequency current was used for the abolition of all abnormal electrograms including FrP, hFrP, LP, frLP.\(^3\)\(^{14,15}\) Subsequently, targeted regions were remapped to demonstrate elimination of the respective electrograms. Radiofrequency current was applied with a maximum power of 40 W (upper temperature limit was set to 48°C) at an irrigation rate of 17–30 ml/min.

2.6 | Statistical analysis

Descriptive statistics are presented as count and percentage for categorical variables and as mean ± standard deviation (SD) or median (interquartile range) for continuous variables. Patient characteristics were compared using student’s t tests. The reported p values are two-sided; p values less than .05 are considered statistically significant. Statistical analyses were
performed using the statistical software GraphPad Prism 7.0 (GraphPad Software Inc.) and R version 3.6.3 (R Foundation for Statistical Computing).

3 | RESULTS

3.1 | Study population

A total of 65 consecutive procedures in 61 patients were analyzed (see Figure 1). Baseline patient characteristics are shown in Table 1. All patients had a cardiomyopathy (ischemic in 37 patients [60.7%]) with a mean left ventricular ejection fraction of 36 ± 12%.

3.2 | Procedural data

The median procedural duration was 201.5 (175.8–240.0) min and the median fluoroscopy duration was 19.0 (15.2–26.0) min. The median radiofrequency duration was 1637 (871–2536) s. In 50 procedures at least one VT was inducible, and two patients presented with ongoing VT at the beginning of the procedure. Twenty-three out of 52 VT were hemodynamically not or only shortly tolerated. LV access with the basket catheter was retrograde in 11, transseptal in 35 and via both approaches in 13 procedures. RV mapping only was performed in six and additional epicardial mapping in four procedures.

3.3 | Ultrahigh-density 3D-mapping

A total of 55 endocardial substrate maps (44 complete) and 44 activation maps during VT (22 complete) were acquired. The mean number of automatically acquired mapping points was 10319 ± 889 for substrate maps. Substrate maps were acquired during SR in 25 out of 55, CS pacing in 13 out of 55 and ventricular pacing in 17 out of 55 patients. Identifying the VT circuit was possible in 23 out of 44 VT maps (9% single loop reentry, 30% double loop reentry, 35% figure-of-eight reentry, 26% focal). Mean number of points was 9053 ± 6283 for activation maps and mean mapping time was 15 ± 2 min. In five patients more than one complete VT was mapped.

3.3.1 | Incidence, distribution and characteristics of abnormal electrograms

Mean low-voltage area (border zone and dense scar, <1.0 mV) was 52 ± 24% and mean dense scar (<0.1 mV) was 9 ± 10% of total mapped LV surface. In all patients with identified VT circuit, the
central common pathway during reentry was related to low-voltage areas (both dense and border zone scar).

FrP were found in all patients, hFrP in 80%, LP in 80%, frLP in 77%, and iLP in 43%. The mean area of abnormal electrograms and number of identified areas is shown in Table 2. FrP (29 ± 18% of total mapped LV area) had the greatest prevalence and variability, iLP (0.8 ± 1.3% of total mapped LV area, Figure 4) the smallest. The percentage of abnormal electrogram area on total low-voltage area is shown in Table 2 and was distributed corresponding to the percentage on total mapped LV area. Voltage maps indicated areas with abnormal electrograms most often in border zone scar (Figure 4). Only in two patients FrP were found in areas with predominantly normal voltage. In the isochronal map, areas of slow conduction during sinus or paced rhythm were found in 64% of substrate maps, most often in border zone scar (86%, 7% in dense scar, 7% normal voltage area; Figure S1).

A subgroup analysis of patients with ischemic and nonischemic cardiomyopathy is shown in Table 2. In brief, patients with ischemic cardiomyopathy had on average larger areas with fractionated and highly fractionated electrograms than patients with nonischemic cardiomyopathy, while the total area with late potentials did not differ.

In two patients with ischemic cardiomyopathy presence and timing of LP was dynamic showing varying conduction properties (both 2:1 block and Wenckebach periodicity). Increasing conduction properties after atropine infusion led to stable presence of LP (Figure 5).

### 3.3.2 Abnormal electrogram characteristics in critical VT areas

A postinterventional analysis of electrograms during sinus or paced rhythm associated to VT circuit showed low-voltage hFrP in all isthmus areas (Table 3, Figure 6, Figure S2). The mean number of fractionations was 10 ± 2 (5–15). The rates of areas with abnormal electrograms matching to VT isthmus were similar in all categories (FrP 33%, hFrP 42%, LP in 35%, frLP in 27% and iLP in 43%). During VT, hFrP showing long duration, covering almost the entire VT CL were found near the exit (Figure 7). iLP during sinus or paced rhythm were found in areas distant from the critical VT isthmus area in 4 out of 14 patients (Figure 8) and associated but not specific in 4 out of 14. Slow conduction during sinus or paced rhythm was found in areas neighboring the critical VT circuit in 12 out of 14 patients, but not specific in 92% (Figure S1). A subgroup analysis of patients with ischemic and nonischemic cardiomyopathy showed that there were no significant differences regarding the type (e.g. FrP/LP) of abnormal signals in the critical VT area. In 2 out of 14 patients a focal VT mechanism was identified (Table 3, Figure S3).

### 4 DISCUSSION

The main findings of the present study are:

1. Depending on the definition of abnormal electrograms (low-voltage, fractionated potentials, late potentials) the potential ablation target area varies enormously in size.
Clear linking between substrate map electrograms and the critical VT isthmus is limited due to a lack of specificity rather than sensitivity.

Highly fractionated potentials were present in all identified VT isthmus sites during substrate mapping and can be rapidly identified by automated annotation. Furthermore, slow conduction on isochronal maps was often found to be associated with these sites.

The latest and isolated late potentials were often found distant from the identified critical VT isthmus.

**4.1 Substrate ablation area**

The definition of myocardial scar is well known to be a key step of any substrate-based ablation approach. The importance of electrogram analysis in this context has been pioneered by Josephson and colleagues, while in recent years novel procedural endpoints involving a combination of low amplitude and several abnormal electrogram characteristics (local abnormal ventricular activities) have become widely used.

We show, that within the low-voltage zone, the size of the ablation target area varies enormously, depending on the definition of abnormal electrograms. Definition only by a low number of fractionations (FrP group) or any appearance after the QRS offset (LP group) resulted in both, a wide critical area and frequent inclusion of borderline electrograms—and is in our opinion less valuable. Many previous studies use inhomogeneous definitions, making procedures and clinical outcome less reproducible and comparable. In addition, previous studies agree with our finding, that only a small proportion of actual abnormal electrograms is located in the region of clinical relevant VT channels. Hence, the ablation area might often be more extensive than necessary using substrate-based approaches. Nevertheless, a recent meta-analysis confirmed, that a complete substrate modification achieves better outcome than a limited substrate modification. This might be due to a lack of the specific link of abnormal findings in SR to the VT isthmus—making elimination of all abnormal electrograms more successful by including both relevant and irrelevant areas. Another reason might be the progressive nature of the underlying structural heart disease. Areas presenting unremarkable at first might transform as myocardial scars develop and change during progress of the cardiomyopathy.

Advances in 3D-mapping systems and catheter techniques, especially higher resolution with an increase in acquired points, have made a very detailed depiction of the substrate possible. However, as for low-voltage area cutoffs, it is not clear if the established criteria can be transferred to these novel conditions, further increasing the difficulty of reproducibility and electrogram identification. The type of cardiomyopathy might be of clinical importance, as fractionated electrograms were detected to a lesser extent in patients with nonischemic cardiomyopathy as shown in our subgroup analysis. A possible reason is a more common midmyocardial or epimyocardial distribution of the often partly patchy substrate in nonischemic cardiomyopathy as shown in our subgroup analysis. A possible reason is a more common midmyocardial or epimyocardial distribution of the often partly patchy substrate in nonischemic cardiomyopathy that might not be detected with an endocardial mapping approach. A substrate of that kind might be more accessible through an epicardial or in some cases bipolar ablation approach. Furthermore, depiction of the myocardial scar by magnetic resonance imaging or computed tomography might be helpful to identify the optimal ablation strategy.

In contrast to first experiences with the Orion catheter, where recorded electrograms were not reproducibly detected
using conventional ablation catheters, we saw more comparable results with the novel mini-electrode ablation catheter (Figure 9). Moreover, complete manual review of all points, at least during the procedure, is challenging but often necessary regardless of the approach. In our experience, identification of areas of interest (e.g., with fractionated or late potentials) with the system’s integrated annotation algorithm enabled subsequent focused manual review in practicable time.

4.2 Specific electrogram characteristics—impact of fractionation and timing

Abnormal electrograms originate in consequence of scarred myocardium where fibrous tissue separates myocardial fibers. The role of these signals as a target for substrate-based ablation was demonstrated by several groups performing initially surgical and in the last two decades catheter-based approaches with reasonable long-term outcome. However, definitions of abnormal electrograms vary and additionally depend on electrode size, spacing, design and the angle of the incident wave front to the mapping catheter. In contrast to previous studies focusing on ultrahigh-density mapping, small interelectrode spacing, optimized signal/noise ratio and automatic detection of abnormal electrograms, we could not show a clear predictive value for one defined electrogram subgroup during substrate mapping as a surrogate for the critical VT area. As it has been reported for LP, this is mostly due to a lack of specificity, rather than sensitivity. Indeed, FrP were found in all patients and hFrP, LP, and frLP were present in approximately 80% of patients. The deficiency of specificity might at least in part be due to a dynamic component of the substrate. Indeed, our findings add evidence
on the dynamicality of the ventricular substrate, which has been previously described in experimental and initial clinical findings. LP showed altered timing both spontaneously and after increasing conduction properties in two patients in our current study. This finding is of clinical relevance, as it implies that the substrate could be displayed differently depending on both the rhythm (SR vs. ventricular or atrial pacing) and the heart rate while mapping. A technique to facilitate the analysis and comparison of maps created in spontaneous and paced rhythm has been recently proposed by our group and might be of interest for future studies.

We found iLP in areas distant from the critical VT isthmus in 29% of patients. This supports the hypothesis, that the latest potentials are not the most specific ones. They might only represent normal late activation during sinus or paced rhythm without being a VT substrate. Therefore, potential duration and conduction velocity might have to be considered instead. In fact, activation duration might be more important than absolute timing. Reports on longer duration of fractionated potentials in clinically relevant VT channels compared to fractionated potentials elsewhere within low-voltage areas further support this. Thus, beyond late potentials, abolishment of early fractionated potentials (e.g., during QRS), as introduced as a procedural endpoint by Jais et al., might be of interest. Furthermore, in our analysis all VT isthmus sites showed fractionated potentials with ten or more fractionations during substrate mapping, emphasizing a possible predictive advantage of higher degree of fractionation. Future investigations have to better characterize these potentials, as they were often not specific.

In line with previous studies, we found areas with isochronal crowding, indicating slow conduction, to be associated with the VT isthmus in most patients. However, isochronal crowding was also found in other low-voltage regions, distant from the isthmus of the clinical VT. Potentially, these areas could also give rise to further VT, which have not become clinically relevant yet. In future, additional criteria are warranted to specify areas with slow conduction.

4.3 | Limitations

This study reports on a single center experience. Due to precise selection criteria (complete substrate map and identified VT isthmus by activation map, not only by entrainment map) some findings relate to only a small sample size and may represent certain VT, as many other were not completely mappable.

We do not provide a prospective validation of specific electrogram characteristics as an ablation target and thus can only generate hypotheses for further studies aiming at a clear identification of substrate map electrograms linking to VT origin. Comparison of different activation wavefronts might additionally improve critical VT isthmus identification and novel approaches like the "one acquisition-two maps" technique might give additional insights. Of note, the exact discrimination between different parts of reentry circuit (entrance or isthmus) was often not possible due to comparably high interpoint distance (>0.25 mm) and a slightly different anatomic shell between maps. However, detailed division is maybe not necessary as recent studies have shown that the dimensions are relatively small.

5 | CONCLUSION

The target area of substrate-based ablation of scar related VT varies enormously in size, depending on the definition of abnormal electrograms. Clear linking between SR electrograms and critical VT reentrant circuit is difficult due to lack of specificity rather than sensitivity. However, highly fractionated, low-voltage electrograms in ultrahigh-density maps can be easily identified by automated annotation with manual revision and were found to be present in all

FIGURE 8 Isolated late potentials distant from VT isthmus. Left ventricular activation (A) and bipolar voltage (B) map. (B) Area with bipolar isolated late potentials (*) during ventricular paced rhythm is highlighted and (A) distant from VT isthmus site. VT, ventricular tachycardia.
critical VT areas. Prospective studies are warranted to further identify specific electrogram characteristics and evaluate them as an ablation target to standardize procedures and improve efficiency.

**DATA AVAILABILITY STATEMENT**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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