Drivers in AF collocate to sites of electrogram organization and rapidity: Potential synergy between spectral analysis and STAR mapping approaches in prioritizing drivers for ablation

Shohreh Honarbakhsh MRCP1 | Richard J. Schilling MRCP, MD1 | Emily Keating BAppSc1 | Malcolm Finlay MRCP, PhD1 | Ross J. Hunter FESC, PhD1,2

1Barts Heart Centre, Barts Health NHS Trust, London, United Kingdom  
2QMUL

Correspondence  
Ross J. Hunter, Barts Heart Centre, Barts Health NHS Trust, W. Smithfield, London EC1A 7BE, United Kingdom.  
Email: ross.hunter@bartshealth.nhs.uk

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Abstract  
Introduction: Stochastic trajectory analysis of ranked signals (STAR) mapping has recently been used to ablate persistent atrial fibrillation (AF) with high rates of AF termination and long-term freedom from AF in small, single-arm studies. We hypothesized that rapidity and organization markers would correlate with early sites of activation (ESA).  

Methods: Patients undergoing persistent AF ablation as part of the STAR mapping study were included. Five-minute unipolar basket recordings used to create STAR maps were used to determine the minimum-cycle length (Min-CL) and CL variability (CLV) at each electrode to identify the site of the fastest Min-CL and lowest CLV across the left atrium (LA). The location of ESA targeted with ablation was compared with these sites. Dominant frequency was assessed at ESA and compared with that of neighboring electrodes to assess for regional gradients.  

Results: Thirty-two patients were included with 83 ESA ablated, with an ablation response at 73 sites (24 AF termination and 49 CL slowing ≥30 ms). Out of these, 54 (74.0%) and 56 (76.7%) colocated to sites of fastest Min-CL and lowest CLV, respectively. Regional CL and frequency gradients were demonstrable at majority of ESA. ESA colocating to sites of fastest Min-CL and lowest CLV were more likely to terminate AF with ablation (odds ratio, 34 and 29, respectively, μ = .02). These showed a moderate sensitivity (74.0% Min-CL and 75.3% CLV) and specificity (66.7% Min-CL and 76.9% CLV) in predicting ESA with an ablation response.  

Conclusions: ESA correlate with rapidity and organization markers. Further work is needed to clarify any role for spectral analysis in prioritizing driver ablation.

Keywords  
atrial fibrillation, catheter ablation, cycle length, localized drivers, spectral analysis

Abbreviations: AF, atrial fibrillation; CL, cycle length; CLV, cycle length variability; DF, dominant frequency; PVI, pulmonary vein isolation; LA, left atrium; LVZ, low-voltage zone; Min-CL, minimum cycle length; STAR, stochastic trajectory analysis of ranked signals.

[Correction added on 27 April 2020, after first online publication: QMUL has been added as an affiliation for the corresponding author]
Evidence is conflicting as to whether electrogram characteristics are useful as surrogate markers for localized drivers in persistent atrial fibrillation (AF) in humans.1-4 Whilst markers of organization have better identified sites that play a mechanistic role in AF,1,7 markers of rapidity have been less reliable.1,2 Optical mapping animal studies have shown that AF is maintained by sites demonstrating fastest cycle lengths (CL) and highest dominant frequency (DF); however, in humans, this has proven to be a poor predictor of localized driver sites.1 The poor correlation may be because of the lack of spatio-temporal stability of drivers in AF, which may explain the apparent inconsistency of sites of rapidity.2,6 In addition, optical mapping animal studies have shown intra-atrial high- to low-frequency gradients at rotor sites.7

A novel mapping strategy called stochastic trajectory analysis of ranked signals (STAR) mapping has recently been used to guide AF ablation, resulting in high rates of AF termination and subsequent freedom from AF.5,11 We hypothesized that using a novel methodology for CL analysis, sites demonstrating greater rapidity and organization would collocate to AF driver sites identified using the STAR mapping method. Furthermore, we hypothesized that the driver sites identified using this approach that did demonstrate greater rapidity and organization would be more mechanistically important in AF maintenance, as evidenced by a greater likelihood of AF termination with ablation.

2 | METHODS

Patients undergoing catheter ablation for persistent AF (<24 months and no previous AF ablation) and that were prospectively included in the STAR mapping study (clinicaltrials.gov NCT02950844) were included (Supporting Information Material). Patients provided informed consent for their study involvement which was approved by the UK National Research Ethics Service (16/LO/1379).

2.1 | STAR mapping method

The STAR mapping method has been described in detail previously.12,13 In brief, the STAR mapping method principle is to use data from multiple individual wavefront trajectories to identify atrial regions that most often precede the activation of neighboring areas. By gathering data from many thousands of activations, a statistical model can be formed. This permits regions of the atrium to be ranked according to the amount of time those activations precede those of adjacent regions (Supporting Information Material).12,13 A STAR map consists of color-coded electrode positions projected on to a replica of the patient’s atrial geometry created in CARTO. Each color represents the proportion of time the electrode spends leading in relation to the other paired electrodes as highlighted by the color scale on the right-hand side of the STAR maps. An early site of activation (ESA) is defined as an electrode leading ≥75% of the time compared with paired electrodes.

2.2 | STAR mapping study

All patients underwent at least two 5-minute unipolar recordings in the left atrium (LA) pre- and post-pulmonary vein isolation (PVI) utilizing a whole-chamber basket catheter (Constellation; Boston Scientific Ltd, Marlborough, MA or FIRMap, Abbott, CA). These recordings were used to create STAR maps. All patients underwent PVI followed by STAR mapping-guided ablation of ESA (Supporting Information Material).13 A study-defined ESA ablation response included AF termination or CL slowing ≤30 ms.

2.3 | Bipolar voltage and ESA (Supporting Information Material)

ESA identified were categorized as existing in either non-–low voltage zone (LVZ) or LVZ. The relationship of ESA mapped to LVZs and achieving AF termination on ablation was assessed. The relationship between the proportion of LVZs and the number of ESA identified was also evaluated.

2.4 | Spectral analysis and ESA

Utilizing the unipolar signals recorded from the basket catheter, the CL was determined at each electrode pole in contact over each of the 5-minute recordings in each patient. The CL was measured as the time difference between two consecutive atrial signals using a custom-written Matlab script (Matlab 2017b; MathWorks, Natick, MA). Predefined refractory periods of 70 ms/12-14 were used to avoid double-counting of fractionated electrograms. Ventricular far-field signals were filtered using a method previously published11 (Supporting Information Material). Unipolar activation timing was taken as the maximum negative deflection (peak negative dv/dt). A minimum voltage cutoff of 0.1 mV was used. All the CL measurements over the 5-minute recording for each electrode was used to create a histogram of the CLs with all CLs identified on the x-axis (rounded to the nearest whole millisecond) and the percentage of recording made up by each CL on the y-axis were plotted for each individual electrode for each 5-minute recording for each patient. The histograms were used to determine the dominant CL and minimum-CL (Min-CL) (Supporting Information Material and Figure S1). The parameters for CL determination was uniform for all the cases. There was no attempt to compensate for spectral leakage or bias. The relationship between ESA and site(s) of the fastest dominant CL, fastest Min-CL, and lowest CL variability (CLV) was assessed (Supporting Information Material and Figure S1). Two definitions of the fastest Min-CL were tested: (a) the Min-CLs within the top decile of all electrodes and/or (b) the single overall fastest Min-CL or
“Absolute Min-CL” and any other point with a Min-CL within 5% of the Absolute Min-CL. The lowest CLV sites were defined as (a) CLVs in the lowest decile and/or (b) CLVs within 5% of the overall lowest CLV, termed the “Absolute lowest CLV.”

2.5 | Regional CL and frequency gradients at ESA

The Min-CL at ESA was compared with the Min-CL obtained at adjacent electrodes to elicit whether there was a CL gradient from ESA to surrounding areas. This was repeated for all ESA identified on each STAR map in each patient. Neighboring electrodes were defined as electrodes that were within 3 cm of the ESA. This was also repeated using DF measurements to assess for frequency gradients from ESA to surrounding areas (Supporting Information Material). The relationship between LA site(s) with the overall highest DF, as per those values in the top decile, and ESA was also assessed.

2.6 | Impact of PVI on spectral analysis data

Offline analysis of STAR maps pre-PVI was performed to determine whether ESA identified post-PVI were present pre-PVI. Using the method described above, the Min-CL and lowest CLV was determined at the ESA using the pre-PVI unipolar recordings. Any impact PVI had on these values were evaluated at ESA that were identified pre- and post-PVI.

2.7 | Statistical analysis

Statistical analyses were performed using SPSS (IBM SPSS Statistics, Version 24; IBM Corp, New York, NY). Continuous variables are displayed as mean ± SD or median (IQR). Categorical variables are presented as a number and percentage. The Student t test, or its nonparametric equivalent, the Mann-Whitney U test when appropriate was used for comparison of continuous variables. Fisher’s exact test was used for the comparison of nominal variables. Sensitivity and specificity were used to determine the predictive power of the proportion of LVZs, rapidity, and organization markers in identifying ESA and particularly those associated with an ablation response. The odds ratio was also calculated to determine the probability of an ESA being associated with an ablation response depending on whether it colocalated or not to spectral analysis markers and LVZs. One-way analysis of variance was used to compare the Min-CL and highest DF changes from an ESA to neighboring poles. Results with P < .05 were regarded as significant.

3 | RESULTS

Thirty-two patients underwent STAR mapping-guided ablation. Baseline characteristics are demonstrated in Table S1. The mean AF duration was 15.4 ± 4.3 months (n = 4 AF duration <12 months and n = 28 AF duration >12 months) and 21 of the 32 (65.6%) patients were on an antiarrhythmic drug preablation. The total procedural radiofrequency (RF) time whilst in AF was 52.1 ± 7.7 minutes. The total RF time to achieve sinus rhythm with ablation (including PV isolation, ESA ablation + AT ablation) was 64.5 ± 9.7 minutes.

3.1 | Ablation response at ESA

In brief, 92 ESA were identified in the 32 patients (2.8 ± 0.8 per patient) on the post-PVI STAR maps of which 83 (90.2%, 2.6 ± 0.7 per patient) were targeted with ablation (Figure 1 and Table S2). The nine ESA that were not ablated were in patients in whom ablation at a previous site had resulted in AF termination. An ablation response was achieved with 73 ESA (2.3 ± 0.6 per patient).
which included at least one response in all 32 patients. On a per ESA basis, AF termination was achieved with ablation at 24 sites (18 organization to AT and 6 termination to sinus rhythm) and CL slowing of ≥30 ms was achieved with 49 sites. On a per patient basis, AF termination was achieved in 24 patients (6 sinus rhythm and 18 AT) and CL slowing of ≥30 ms in the remaining 8 patients.

### 3.2 | Bipolar voltage and ESA

On a per patient basis, an average of 2.5 ± 0.6 well-defined LVZs were identified. A majority of the ESA identified were mapped to LVZs (62/92, 67.4%). Out of the 83 ESA that were ablated, 60 were mapped to LVZs (72.3%) of which 59 (98.3%) were associated with an ablation response.

Patients with more than 50% of the LA comprised of LVZs (59.2 ± 6.5 mV) were more likely to have more than two ESA identified. There was a strong positive correlation between the proportion of LVZs present and the number of ESA identified ($r_s = 0.91; P < .001$). However, LVZ alone was of little predictive value in predicting ESA (Table S2).

The association of ESA with an LVZ was highly predictive of an ablation response (Table 1). ESA mapped to LVZs were also more frequently associated with AF termination on ablation vs ESA mapped to non-LVZs (odds ratio = 20.0, 95% confidence interval [CI], 1.1-351.5; $P = .04$).

### 3.3 | Spectral analysis and ESA

For the spectral analysis, a total of 170 5-minute unipolar recordings were used. The mean dominant CL and the mean Min-CL obtained at ESA post-PVI were 137.9 ± 64.2 ms and 131.2 ± 15.5 ms, respectively.

### 3.4 | Colocation of sites identified on spectral analysis and ESA

#### 3.4.1 | Fastest dominant CL

Of the 92 ESA identified post-PVI, 47 (51.1%) colocated to the site of the fastest dominant CL(s). Dominant CL showed a sensitivity of 51.1% (95% CI, 40.4-61.7%) and specificity of 18.6% (95% CI, 8.4-33.4%) in predicting ESA. The positive and negative predictive values were 57.3% (95% CI, 51.2-63.2%) and 15.1% (95% CI, 8.4-25.6%), respectively.

#### 3.4.2 | Min-CL sites within the top decile and 5% of the “Absolute Min-CL”

On a per patient basis, an average of 3.0 ± 0.8 and 2.0 ± 0.7 Min-CL sites were identified in the top decile and within 5% of the Absolute Min-CL, respectively. Of the 92 ESA identified post-PVI, 58 (63.0%) and 56 (60.9%) colocated to one of these sites, respectively. These markers were of little predictive value in predicting ESA (Table S3).

### Table 1

|         | Min-CL (%) | Lowest CLV (%) | LVZ (%) |
|---------|------------|----------------|---------|
|         | n (%)      | n (%)          | n (%)   |
| Top decile | n (%)      | n (%)          | n (%)   |
| Within 5% | n (%)      | n (%)          | n (%)   |
| Lowest decile | n (%)      | n (%)          | n (%)   |
| Within 5% | n (%)      | n (%)          | n (%)   |
| ESA (out of 73 ESA) | 54 (74.0) | 54 (74.0) | 56 (76.7) | 55 (75.3) | 59 (80.8) |
| Patients with at least one ESA with an ablation response correlating (out of 32 patients) | 29 (90.6) | 29 (90.6) | 29 (90.6) | 29 (90.6) | 29 (90.6) |
| Prediction of ESA with an ablation response % (95% CI) | Sensitivity | 74.0 (62.2-83.2) | 74.0 (62.2-83.2) | 76.7 (65.1-85.8) | 75.3 (63.6-84.4) | 80.8 (69.6-88.8) |
| Specificity | 23.8 (12.6-39.8) | 66.7 (38.7-87.0) | 27.0 (14.4-44.4) | 76.9 (46.0-93.8) | 38.5 (20.9-59.3) |
| PPV | 62.8 (51.6-72.8) | 91.5 (80.6-96.8) | 67.5 (56.2-77.1) | 94.8 (84.7-98.7) | 78.7 (67.4-87.0) |
| NPV | 34.5 (18.6-54.3) | 34.5 (18.6-54.3) | 37.0 (20.1-57.5) | 35.7 (19.3-55.9) | 41.7 (22.8-63.1) |
| False positives n % | 32 (37.2) | 5 (8.5) | 27 (32.5) | 3 (5.2) | 16 (21.3) |

Notes: It also shows the diagnostic accuracy of these parameters in predicting ESA with an ablation response. Abbreviations: CI, confidence interval; CL, cycle length; CLV, cycle length variability; ESA, early sites of activation; NPV, negative predictive values; PPV, positive predictive values; PVI, pulmonary vein isolation; LVZ, low-voltage zones.

*Min-CL- sites with Min-CL at the top decile of the fastest Min-CL.

*Min-CL- sites with Min-CL within 5% of the Absolute fastest Min-CL.

*Lowest CLV- sites with CLV at the lowest decile of the lowest CLV.

*Lowest CLV- sites with CLV within 5% of the Absolute lowest CLV.
3.4.3 | Lowest CLV sites within the lowest decile and 5% of the “Absolute lowest CLV”

On a per patient basis, an average of 2.9 ± 0.8 and 2.0 ± 0.7 lowest CLV sites were identified in the lowest decile and within 5% of the Absolute lowest CLV, respectively. Of the 92 ESA identified post-PVI, 61 (66.3%) and 60 (65.2%) colocated to one of these sites, respectively. The predictive power of this parameter in identifying ESA is demonstrated in Table S3.

3.5 | Use of spectral analysis to predict response to ablation at ESA

3.5.1 | Fastest dominant CL

Of the 73 ESA with an ablation response, only 39 (53.4%) colocated to the fastest dominant CL sites. The fastest dominant CL showed a sensitivity of 53.4% (95% CI, 41.4-65.2%) and specificity of 26.3% (95% CI, 13.4-43.1%) in predicting ESA. The positive and negative predictive values were 58.2% (95% CI, 51.1-65.0%) and 22.7% (95% CI, 14.1-34.6%), respectively.

3.5.2 | Min-CL sites within the top decile and 5% of the “Absolute Min-CL”

Of the 73 ESA with an ablation response, 54 (74.0%) colocated to one of the fastest Min-CL sites by either definition (Figures 1 and 2A-F). The predictive power of these parameters in identifying ESA with an ablation response is demonstrated in Table 1.

3.5.3 | Lowest CLV sites within the lowest decile and 5% of the “Absolute lowest CLV”

Of the 73 ESA with an ablation response, 56 (76.7%) colocated to one of the lowest CLV sites as defined within the lowest decile (Figures 1 and 2A-F). The predictive power of this parameter in identifying ESA with an ablation response is demonstrated in Table 1.

FIGURE 2  (A-F), Patient ID 6. (A) STAR map of the LA in a titled roof view that shows an ESA mapped to mid roof. (B) A CL map in a titled roof view demonstrates the overall fastest Min-CL at the mapped ESA. (C) A CLV map in a titled roof view demonstrates the lowest CLV at the mapped ESA. The CL and CLV maps were created by projecting basket electrode positions onto the replica geometry in Matlab. Rather than presume to interpolate between points as is conventional for a voltage map, a 10-mm radius of color surrounds the points with increasing transparency towards the edges, or a blurred edge where boundaries meet. (D) Electrograms obtained at the ESA identified on the STAR map (highlighted by the star) and neighboring electrodes as assigned by the STAR mapping method. The electrograms obtained at the ESA demonstrates that this site is leading in comparison to its neighboring pairs and also has a faster CL. (E) CARTO map of the LA in a roof view that demonstrates ablation at the ESA as guided by the STAR map. (F) Electrograms shows the termination of AF to sinus rhythm on ablation at the ESA. ESA, early sites of activation; LA, left atrium; STAR, stochastic trajectory analysis of ranked signals.
3.5.4 | Predicting AF termination

ESA that colocated with fastest Min-CL sites as per either definition were more frequently associated with AF termination on ablation in contrast to CL slowing (24/24 (100%) vs 29/49 (59.2%); \( P < .001 \)). This marker showed an odds ratio of 34.1 (95% CI, 2.0-592.3; \( P = .02 \)) for predicting AF termination on ablation at an ESA.

ESA that colocated with lowest CLV sites as per either definition were more frequently associated with AF termination on ablation in contrast to CL slowing (24/24 (100%) vs 31/49 (63.2%); \( P < .001 \)). This marker showed an odds ratio of 28.8 (95% CI, 1.7-501.6; \( P = .02 \)) for predicting AF termination on ablation at an ESA.

3.6 | Regional CL and frequency gradients and ESA

Of the 92 ESA identified, there was a clear gradient in Min-CL from the ESA to the surrounding poles with 56 ESA (60.9%) (Figures 1 and 3A-C). Of the 73 ESA with an ablation response, 61 (83.6%) demonstrated a fastest-slowest Min-CL gradient from the ESA to neighboring poles. The mean reduction in Min-CL was 10.5 ± 4.2 ms (\( P = .01 \)). The presence of a regional CL gradient at ESA showed an odd ratio of 5.1 (95% CI, 1.3-20.3; \( P = .02 \)) in predicting ESA with an ablation response.

The mean DF in the LA was 5.9 ± 0.8 Hz. The mean DF at the ESA was 6.2 ± 0.7 Hz. ESA only colocated to sites of highest DF in the LA in 56.5% of cases (52/92) of which 41 out the 73 (56.2%) with an ablation response colocated to sites of highest DF. Of the 92 ESA identified, there was a clear frequency gradient from the ESA to the neighboring poles with 59 ESA (64.1%) (Figures 1 and 4A-C) with a mean reduction in DF of 1.8 ± 0.7 Hz (\( P = .01 \)). When only reviewing the 73 ESA with an ablation response, 58 (79.5%) demonstrated a frequency gradient.

3.7 | Impact of PVI on spectral analysis data

Of the 92 ESA that were identified post-PVI, 42 were also detected on the pre-PVI maps of which 39 (92.9%) were associated with a study-defined ablation response. All ESA identified on the pre-PVI maps were also seen on the post-PVI maps. The mean CLV pre-PVI (obtained through taking the average CLV of all electrodes) was lower in those patients that had ESA identified both pre-PVI compared with those that only had ESA identified post-PVI (31.4 ± 4.8 ms vs 49.5 ± 7.3 ms; \( P = .01 \)).

PVI did not affect the CL (131.0 ± 12.1 ms pre-PVI vs 131.2 ± 15.5 ms; \( P = .96 \) post-PVI) and CLV (10.3 ± 3.9 ms pre-PVI vs 11.0 ± 5.4 ms post-PVI; \( P = .80 \)) at the ESA.

ESA that were also identified pre-PVI showed a sensitivity of 53.4% (95% CI, 41.4-65.2) and specificity of 90.0% (95% CI, 55.5-99.8) in predicting ESA with an ablation response. The positive and negative predictive value was 97.5% (95% CI, 85.7-99.6) and 20.9% (95% CI, 16.1-26.7), respectively.

4 | DISCUSSION

This study has demonstrated that sites of rapidity (identified using Min-CL) and organization (identified using CLV) are associated with ESA in terms of colocating. Although this association was unlikely to

**FIGURE 3** (A-C). Patient 16. (A) STAR map of the LA in a titled lateral view that shows an ESA. (B) Ablation was performed at this site as demonstrated on the CARTO LA map in a titled lateral view which resulted in termination of AF into AT. (C) The ESA colocated to the site of regional fastest CL with a reduction in CL as obtained from neighboring electrodes. The CL map was created by projecting basket electrode positions onto the replica geometry in Matlab. Rather than presume to interpolate between points as is conventional for a voltage map, a 10-mm radius of color surrounds the points with increasing transparency towards the edges, or a blurred edge where boundaries meet. AF, atrial fibrillation; CL, cycle length; CLV, cycle length variability; ESA, early sites of activation; LA, left atrium; STAR, stochastic trajectory analysis of ranked signals.
be sufficient to accurately identify driver sites in itself. ESA that did correspond to areas of rapidity and organization using these novel markers were much more likely to have an ablation response suggesting the potential for synergy in their use. Peaks in DF showed limited association with ESA. However, the demonstration of a clear gradient in DF and CL to surrounding areas was demonstrated at a majority of ESA. ESA were identified pre-PVI in patients with more organized AF as evidenced by longer CL and less CLV. The characteristics of ESA sites identified before PVI were unchanged following PVI suggesting that these sites are unaffected by PVI. ESA were predominantly mapped to LVZs and the degree of LVZs was predictive of the number of ESA identified. ESA mapped to LVZs were also more frequently associated with AF termination on ablation in contrast to those that were not.

4.1 | Spectral analysis and ESA

This study has shown that approximately 75% of ESA with an ablation response colocated to sites of lowest CLV or to sites of
fastest Min-CL. These parameters showed a reasonable sensitivity and specificity in identifying ESA with an ablation response. Our group has previously shown that AF drivers frequently colocalize to sites of lowest CLV.\textsuperscript{1,7} Other studies have also shown that AF termination is more common in patients with higher baseline organization index.\textsuperscript{15,16}

The data are, however, conflicting in regard to markers of rapidity. Some studies have shown that targeting sites of highest DF is associated with electrophysiological endpoints on ablation\textsuperscript{27} and have promising long-term success rates\textsuperscript{17,18} whilst others have shown that DF-guided ablation in addition to PVI do not result in a significant increment in freedom from AF during follow-up when compared to PVI alone.\textsuperscript{19} This study has shown that ESA poorly colocalized to sites of fastest CL when using the conventional approach for determining fastest CL sites. Our group has previously demonstrated that drivers showing a high degree of temporal stability and a high recurrence rate were more likely to correlate with conventional markers of rapidity such as CL or DF.\textsuperscript{1} Our proposed explanation for this finding was that as the conventional methodology utilized the dominant CL or DF at each electrode, the correlation with driver sites is then dependent on whether the driver is present enough of the time that its CL represents the dominant CL. It is not surprising that there is a lack of correlation given the intermittent nature of the drivers observed. Therefore, in the current study, we opted to compare the Min-CL at each electrode rather than the dominant CL. The logic being that the Min-CL at a driver site ought to better reflect the CL of the driver, and ought to be faster than other sites regardless of the driver’s temporal stability or recurrence rate. This was borne out in that a larger proportion of ESA colocalized to sites of fastest Min-CL compared to that for dominant CL. This variant on conventional CL analysis may, therefore, be a better surrogate marker for driver sites. Defining the fastest Min-CL sites as Min-CLs within 5\% of the Absolute Min-CL was associated with greater specificity in identifying a driver site than when using the top decile.

Even though spectral analysis data showed an association with ESA, the strength of that association is unlikely to enable identification of driver sites in itself. However, ESA that colocalized with these novel markers of rapidity and organization were much more likely to terminate AF on ablation (odds ratio, 29 for lowest CLV and 34 for fastest Min-CL). This suggests that these markers could potentially be of use to aid in differentiating localized drivers that are critical for the maintenance of AF from those that are less mechanically important. These markers could, therefore, potentially be useful for stratifying the importance of ESA, potentially allowing a hierarchal approach to ablation of localized drivers.

4.2 Regional CL and DF gradients and ESA

Studies have shown the presence of a left to right atrial gradient in the context of AF\textsuperscript{20,22} and that PVI results in a loss of this gradient.\textsuperscript{20} However, others have demonstrated an absence of left to right atrial gradients in persistent AF\textsuperscript{22} or in the context of drivers outside the PVs.\textsuperscript{23} In animal studies, regional DF gradient have been reported at sites of rotor activity; however, the presence of intra-atrial gradients has not been assessed in human studies. This is the first study that has demonstrated the presence of regional CL and DF gradients at sites of localized drivers in AF. Due to the conflicting evidence seen with regard to DF ablation and the poor correlation between sites of highest DF in the atrium and localized drivers, this finding highlights that even though localized drivers do not reliably colocalize to the sites of highest DF, as defined using the current methodology to calculate DF, drivers sites do represent sites of highest regional DF. This suggests that rather than comparing DF across the whole atrium to identify sites of highest DF, it may instead be feasible to use DF to look for a regional frequency gradient. Applying this strategy in guiding AF ablation needs to be prospectively evaluated to determine whether it is additive in clinical practice.

4.3 Impact of PVI

The lack of PVI impact on spectral characteristics at driver sites highlights their independence from the PVs. However, as we have shown that drivers are more likely to be identified post-PVI\textsuperscript{1,13,14,24} and with studies demonstrating that PVI eliminates wavebreaks and organizes wavefronts,\textsuperscript{25} this does clearly still highlight the importance of PVI in the ablation strategy for persistent AF. However, these data suggest that they may be less important for the maintenance of AF than the drivers identified as ESA.

4.4 Bipolar voltage and ESA

This study has shown that ESA were predominantly mapped to LVZs and that the proportion of LVZs strongly correlated to the number of ESA identified. These findings are supported by sites of structural remodeling resulting in alteration in CV dynamics that promote re-entrant mechanisms\textsuperscript{26,27} and that reentrant activity anchors to sites of structural heterogeneity.\textsuperscript{28} The bipolar voltage map can thereby be used by the operator to plan the extent of their ablation.

4.5 Limitations

In this study, ESA was used as a surrogate for localized drivers in AF and the focus was on EP endpoints to determine the mechanistic significance of these sites since there is arguably no other way to verify that a driver has been mapped. Others have used AF termination or CL prolongation as a surrogate for the interruption of mechanisms important for AF maintenance.\textsuperscript{16,24,29} Our previous work has shown that targeting these sites prospectively is associated with a high freedom from AF/AT supporting their mechanistic role in AF.\textsuperscript{13}

A 5-minute recording duration was used for the initial study using STAR mapping and for the spectral analysis. However, our group has subsequently shown that drivers can be identified on STAR maps...
using a 30-second recording, thereby allowing for a shorter recording duration. Similarly, studies utilizing other technologies have used much shorter recording periods, and it may, therefore, be possible to conduct spectral analysis with equivalent recording times.  

5 | CONCLUSIONS

Although ESA do not correlate with conventional measures of CL or DF, sites with fastest Min-CL and lowest CLV frequently collocate to ESA with an ablation response particularly AF termination. Regional analysis of CL and DF to look for CL and DF gradients may also be a viable method for demonstrating the presence of drivers and warrants further exploration. These markers may be useful in refining other mapping techniques such as the STAR mapping method and furthermore may help to determine the relative importance of driver sites and hence help to prioritize areas for ablation. Randomized studies are needed to test the clinical utility of these parameters in guiding AF ablation.

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CONFLICT OF INTERESTS

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ORCID

Shohreh Honarbakhsh http://orcid.org/0000-0003-0081-5739

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.