Journal of Molecular and Cellular Cardiology Plus 7 (2024) 100064

Contents lists available at ScienceDirect

Journal of Molecular and Cellular Cardiology Plus

journal homepage: www.journals.elsevier.com/journal-of-molecular-andcellular-cardiology-plus

Selecting repetitive focal and rotational activation patterns with the highest probability of being a source of atrial fibrillation

Ben J.M. Hermans [a,b,*,1], Ozan Özgül [a,1], Michael Wolf [c], Victor G. Marques [a], Arne van Hunnik [a], Sander Verheule [a], Sevasti-Maria Chaldoupi [b], Dominik Linz [b], Milad El Haddad [c], Mattias Duytschaever [c], Pietro Bonizzi [d], Kevin Vernooy [b], Sébastien Knecht [c], Stef Zeemering [a], Ulrich Schotten [a,b]

[a] Department of Physiology, Cardiovascular Research Institute Maastricht (CARIM), University Maastricht, Maastricht, the Netherlands
[b] Department of Cardiology, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Center, Maastricht, the Netherlands
[c] Department of Cardiology, AZ Sint-Jan Brugge, Bruges, Belgium
[d] Department of Advanced Computing Sciences, Maastricht University, Maastricht, the Netherlands

ARTICLE INFO

Keywords:
Atrial fibrillation
Electro-anatomical mapping
AF sources
Ablation

ABSTRACT

Introduction: Repetitive focal and rotational activation patterns are currently used as additional ablation targets for atrial fibrillation (AF). However, there is no evidence that all these detected targets are actual sources of AF. In this paper, we present an approach that detects and ranks AF activation patterns not only based on the degree of pattern repetitiveness but also on the extent to which they are able to entrain their vicinity. This new technique might enable selecting the site with the highest probability of being a source for AF.

Methods: We retrospectively analyzed high-density bi-atrial sequential mapping in ablation-naive persistent AF patients ($n = 13$, PentaRay catheter, 30s recordings). Repetitive focal and rotational activation patterns were detected based on local activation time annotation of unipolar electrograms. The spatial stability was determined as local repetitive pattern duration. The entrainment capability was defined as the average time a directionally coherent repetitive activation pattern was observed in adjacent recordings.

Results: A total of 459 recordings were analyzed (35 ± 5 per patient). We detected 131 repetitive focal (10 ± 4 per patient) and 56 rotational activation patterns (4 ± 3 per patient) in total. Focal patterns were more repetitive than rotational patterns (median [IQR] 0.7 [0.4–1.3] seconds vs. 0.5 [0.4–0.6] seconds, $p < 0.001$ Mann-Whitney *U* test). By applying a 90th percentile threshold to both local and directionally coherent adjacent repetitiveness, we identified 10 sites (9 focal and 1 rotational) in 7 patients as the most probable sources. The majority of these sites were in the upper right atrium or left pulmonary vein region. Notably, in 6 patients (46 %), no probable sources were detected using this threshold.

Conclusion: This study introduces a novel technique to select the repetitive focal or rotational pattern with the highest probability of being a source. We observed that only a minority of repetitive focal or rotational patterns seem to be able to entrain their vicinity and thereby are likely to serve as sources of AF.

1. Introduction

The treatment of atrial fibrillation (AF) by catheter ablation remains a challenge in the field of cardiac electrophysiology. Unlike stable arrhythmias, AF's irregular nature makes it difficult to map the atrium-wide underlying activation patterns with a resolution that is high enough to identify AF ablation targets. Consequently, despite being introduced years ago, pulmonary vein isolation (PVI) still stands as the primary approach for AF ablation, albeit with a limited success rate of approximately 71 % in patients with persistent AF [1].

Recently, there has been growing interest in detecting and utilizing repetitive atrial activation patterns (RAAP) during AF to identify

* Corresponding author at: Department of Physiology, Maastricht University, PO Box 616, 6200MD Maastricht, the Netherlands.
E-mail address: ben.hermans@maastrichtuniversity.nl (B.J.M. Hermans).
@HermansBJM (B.J.M. Hermans)
[1] Both authors contributed equally.

https://doi.org/10.1016/j.jmccpl.2024.100064
Received 28 September 2023; Received in revised form 8 January 2024; Accepted 2 February 2024
Available online 3 February 2024

additional ablation targets. This interest has given rise to the development of the CARTOFINDER algorithm, designed to detect repetitive focal and rotational activation patterns in sequential recordings with the PentaRay catheter [2,3]. While initial results regarding the acute impact on AF cycle length (AFCL) or termination by ablation of the identified drivers through CARTOFINDER appeared promising [3–6], the algorithm has not gained widespread acceptance and adoption within the community [7,8]. This might be caused by the high number of 'drivers' that is typically found by the algorithm [9]. Furthermore, there is no evidence that every repetitive focal or rotational activation pattern is important in the maintenance of AF and, consequently, is to be considered a meaningful ablation target. Therefore, in this study, we propose an innovative technique that does not only detect repetitive focal and rotational activation patterns but also assesses their ability to entrain their vicinity. We hypothesize that true AF drivers are likely to entrain their vicinity and that this feature could increase the specificity of the detection of repetitive activation patterns that indeed act as drivers of AF.

In this paper, we present an extension to the CARTOFINDER algorithm designed to enhance the specificity of AF driver detection. We hypothesize that repetitive spatiotemporally stable AF sources should be able to entrain their vicinity to drive AF. Consequently, our algorithm investigates whether repetitive patterns in the vicinity of source-like activation patterns (focal or rotational) can be linked to the source-like activation pattern based on their conduction direction. According to our hypothesis, source-like activation patterns exhibiting directionally coherent repetitive activation patterns in their vicinity are more likely to be genuine drivers of AF. Conversely, source-like activation patterns lacking directionally coherent repetitive activation patterns in their vicinity are most likely no meaningful ablation targets, as they do not appear to entrain their surroundings. In this paper we aim to introduce our innovative approach and present an initial analysis of a retrospective dataset of 13 persistent AF patients.

2. Material and methods

2.1. Retrospective dataset

We retrospectively reanalyzed an existing dataset of unipolar high-density bi-atrial sequential mapping in ablation-naive persistent AF patients ($n = 13$) that has previously been published by Wolf et al. [9]. In short, unipolar electrograms (EGMs) were collected from both the left (LA) and right atrium (RA) using a PentaRay catheter with 2–6-2 mm interelectrode distance (Biosense Webster Inc.). Each location was mapped for 30 s at sequential PentaRay positions, with each position overlapping the previous recording position to ensure a uniform spread of locations. The total recording time for these high-density bi-atrial maps was 44 ± 6 min [9]. The original study was approved by the Institutional Ethics Committee of the Sint-Jan Hospital in Bruges (BE). Data was anonymized before being transferred from the Sint-Jan Hospital to the Maastricht University (NL).

2.2. Local activation time detection

Local activation times (LAT) were detected by utilizing both bi- and unipolar electrograms similar to the CARTOFINDER algorithm. Our automated annotation of unipolar electrograms has been described previously [10]. Briefly, far-field ventricular signals visible in the atrial recordings were detected and removed using single beat QRST-template cancellation. Candidate LATs were detected using unipolar deflection template matching and classified as actual local activations using a probabilistic algorithm based on the estimated distribution of the AFCL. To avoid false LAT detections due to far-field effects on unipolar electrograms, we chose LATs that also demonstrated activity in bipolar electrograms.

2.3. Detection of source-like activation patterns

Source-like activation patterns (i.e. repetitive focal or rotational activation patterns) were detected similar to the CARTOFINDER algorithm, see Fig. 1A. A repetitive rotational activation pattern was detected if a unidirectional circular activation sequence was observed on at least 4 splines of the mapping catheter that covered >50 % of the acquisition AFCL for at least three consecutive repetitions. A repetitive focal activation pattern was defined as a radial spread of activation originating from one of the center electrodes, conducting to at least 10 (out of 20) other electrodes, and repeated this for at least three consecutive cycles.

For all source-like activation patterns, we determined the local repetitiveness (in % of recording) as a measure of the pattern's stability. This value was obtained by dividing the total number of repetitions by the total number of cycles over the recording. Typically, CARTOFINDER recordings last for 30 s, but if stability is lost, the recording stops automatically. Therefore, we measured the local repetitiveness in relation to the recording duration rather than as an absolute time.

2.4. Entrainment assessment

To assess to what extent source-like activation patterns entrained their vicinity, we searched for any RAAP in adjacent recordings that could be associated with these source-like activation patterns. Adjacent recordings were selected based on the core-to-core distance between catheter positions, see Fig. 1B. Recurrence plots based on the LATs were constructed to detect time intervals containing any RAAPs in these adjacent recordings, as described earlier by our group [11]. The average preferential conduction velocity vectors of all detected RAAPs were then calculated as described earlier [12,13]. Briefly, conduction vectors for each electrode during the time course of the RAAP were calculated through the triangulation method. These conduction vectors were then averaged to reflect an average conduction direction associated with the RAAP, but only when these vectors exhibited directional consistency (circular variance lower than 0.5). This approach allowed us to maintain a limited range of directional variability and avoid calculating an average conduction vector when averaged vectors are divergent. The angles (β) between the theoretical direct conduction path (a vector between the cores of the recording sites) and the averaged preferential conduction vectors associated with all RAAPs were calculated. A small β indicates a high probability that the adjacent RAAP is connected to the source-like activation pattern. Adjacent RAAPs with a β below a predefined threshold were annotated as directionally coherent. This procedure was repeated for all the RAAPs within each adjacent recording, leading to percentages of times where directionally coherent RAAPs were observed at each adjacent recording. The average percentage of time was used as the associated entrainment of the source-like activation pattern (see Fig. 1C). This methodology was applied to all source-like activation patterns.

2.5. Parameter selection for entrainment assessment

The above-mentioned entrainment assessment depends on several parameters. We therefore conducted a sensitivity test to determine the maximum allowed distance between recording sites and the maximal β to determine the directional coherence of RAAPs in the vicinity. As the maximum allowed β increases, the number of detected source-like patterns rises due to reduced directional selectivity. Similarly, a larger maximum allowed distance results in an increased number of detections of source-like patterns because more adjacent recordings are included in the analysis. We have searched for a parameter combination with a reasonably large number of entraining source detections while staying within physiologically acceptable limits for the selected parameters. The maximum allowed distance and β were varied between 0 to 40 mm and 0 to 120 degrees, respectively. The upper values for these parameters

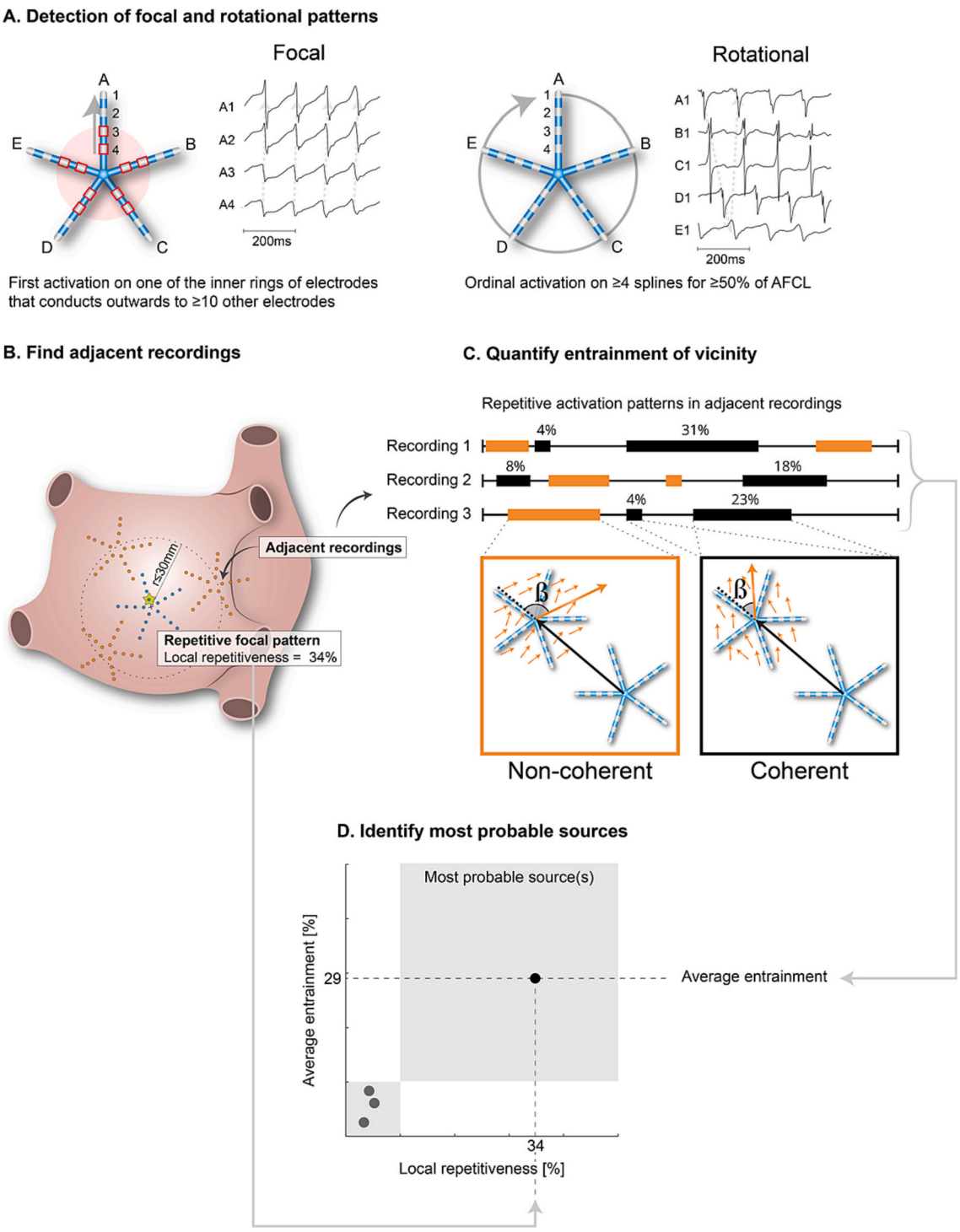

Fig. 1. The proposed repetitive activation pattern and entrainment quantification framework. A Focal and rotational activation patterns that last ≥3 cycles were detected on each recording site. Localized repetitiveness of these patterns was recorded as the percentage of the cycles where this driver was observed. B Recording sites within a 30 mm radius of the initial site were identified and annotated as adjacent recordings. C All detected repetitive atrial activation patterns (RAAP) in the vicinity were classified as directionally coherent if their conduction vectors directed away from site of the repetitive focal or rotational pattern with a small angle (β). The percentages of the recording duration with a directionally coherent RAAP were averaged among each adjacent recording to quantify the entrainment. D The most probable sources were defined as those patterns with high local repetitiveness and entrainment.

were chosen to match the twice diameter of the PentaRay at maximum coverage and to allow rotations around the detected source as observed in spiral wave reentries, respectively. For each parameter combination, we counted the number of focal and rotational activation patterns that exhibited at least 5 % local repetitiveness and entrainment. The reasoning behind setting a threshold of 5 % was to exclude short-lasting focal and rotational activation patterns, which have a low probability of being a source.

2.6. Selecting the most probable sources

In order to find the most probable sources, repetitive focal and

rotational activation patterns were ranked on their probability of being a true driver of AF. Fig. 1D shows the pattern's stability (local repetitiveness) on the horizontal axis and the average entrainment on the vertical axis. Following our hypothesis, true drivers are likely to have a high local repetitiveness and high average entrainment of the vicinity. Therefore, all source-like activation patterns that are located in the right-upper quartile have the highest probability of being a true driver. Those clustered in the left-lower quartile have the lowest probability of being a driver. For this retrospective dataset, we used an arbitrary threshold value equal to the 90th percentile of the local repetitiveness of all source-like activation patterns over all patients to select probable sources (i.e., repetitive focal or rotational activation patterns with a high probability of being a source). Further investigation is required to determine whether a single threshold for repetitiveness can be applied universally to all patients. This paper exclusively utilizes the acquired threshold to demonstrate the potential functionality of this technique in future applications.

To assess the spatial distribution of the source-like activation patterns, the biatrial surface was divided into seven regions: (1) superior RA (SRA) including right atrial appendage, (2) inferior RA (IRA), (3) interatrial septum, (4) LA anterior wall (LA AW), (5) left pulmonary veins (LPV) including left atrial appendage, (6) LA posterior wall (LA PW) and (7) right pulmonary veins (RPV). Every mapped location was manually assigned to one of these regions to allow studying the spatial distribution of the results. Type, number, location, duration, local repetitiveness and RAAP cycle length (RAAPCL) were determined for every source-like activation pattern.

2.7. Statistical analyses

All values are expressed as mean ± standard deviation or median and [interquartile range] depending on the distribution. Differences among properties of repetitive patterns for different anatomical regions were analyzed by the Mann-Whitney *U* test and Kruskal-Wallis test with a Bonferroni post-hoc test to account for multiple comparisons.

3. Results

3.1. Source-like activation patterns

A total of 459 recordings were analyzed (35 ± 5 per patient). We detected 131 repetitive focal (10 ± 4 per patient) and 56 rotational activation patterns (4.31 ± 3.15 per patient) in total. Repetitive focal activation patterns lasted longer than rotational ones (0.7 [0.4–1.3] seconds vs. 0.5 [0.4–0.6] seconds, $p < 0.001$). There were no significant differences in RAAPCLs between repetitive focal and rotational activation patterns (166 [156–184] milliseconds vs. 168 [152–184] milliseconds, $p = 0.630$).

The spatial distribution of all source-like activation patterns is shown in Table 1. The Kruskal-Wallis with Bonferroni post-hoc tests revealed significant differences in focal activation patterns between regions. Specifically, LPV exhibited a higher number of focal activation patterns compared to both LA PW and IRA (3.00 [2.00–4.00] vs. 1.00 [0.75–1.25] and 1.00 [0.00–1.00] respectively, $p = 0.039$ and $p = 0.005$). Additionally, the RAAPCL of focal activation patterns in the LA AW was significantly shorter than in IRA (143 [140–159] milliseconds versus 188 [161–202] milliseconds, $p = 0.044$). No difference was detected between the duration of the focal activation patterns between regions. Regarding rotational activation patterns, no significant differences were observed in terms of their number, duration, or RAAPCL between regions.

3.2. Parameter selection

Fig. 2 shows the influence of the maximal allowed β (horizontal axis) and the maximum allowed distance between recordings (vertical axis) on the number of focal (left) and rotational patterns (right) with at least 5 % local repetitiveness and entrainment for all patients. The lower row displays the impact of varying repetitiveness threshold values on the number source-like patterns (left: focal, right: rotational). As the repetitiveness threshold values increase, the number of probable sources decreases accordingly.

Based on these analyses we utilized a maximum allowed distance of 30 mm for both focal and rotational activation patterns. The maximal allowed β was set at 60 degrees for focal activation patterns and 105

Table 1
Distribution of source-like activation patterns in different regions among patients Data represented as median with [interquartile range]. No., number; RAAPCL, repetitive activation pattern cycle length; s, seconds; ms, milliseconds; SRA, superior right atrium; IRA, inferior right atrium; LA, left atrium; AW, anterior wall; PW, posterior wall; LPV, left pulmonary veins; RPV, right pulmonary veins. * and ** indicate significant difference between regions with $p < 0.05$ and $p < 0.01$ respectively.

	Total	SRA	IRA	Septum	LA AW	LPV	LA PW	RPV
All								
No. [−]**	15.0 [9.8–18.5]	3.0 [2.0–4.3]	1.0 [0.0–2.0]	1.5 [0.0–4.0]	0.0 [0.0–2.0]	3.0 [2.0–5.3]	2.0 [1.0–3.0]	1.0 [1.0–2.5]
Duration [s]	0.56 [0.43–1.07]	0.69 [0.46–1.20]	0.52 [0.44–0.88]	0.44 [0.41–0.70]	0.45 [0.39–1.21]	0.74 [0.43–1.28]	0.56 [0.43–0.89]	0.53 [0.41–1.04]
RAAPCL [ms]	167 [155–184]	174 [163–199]	171 [161–193]	173 [164–184]	145 [140–175]	165 [152–180]	164 [147–179]	164 [156–175]
Focal								
No. [−]**	11.0 [5.0–13.3]	2.0 [1.0–3.3]	1.0 [0.0–1.0]	0.5 [0.0–2.0]	1.0 [0.0–2.0]	3.0 [2.0–4.0]	1.0 [0.8–1.3]	1.0 [0.8–2.3]
Duration [s]	0.74 [0.42–1.26]	0.81 [0.41–1.76]	0.65 [0.48–1.09]	0.42 [0.41–0.79]	0.45 [0.39–1.21]	0.80 [0.45–1.62]	0.89 [0.48–1.03]	0.62 [0.41–1.33]
RAAPCL [ms]*	166 [156–184]	167 [160–197]	188 [161–202]	176 [169–184]	143 [140–159]	164 [153–180]	164 [144–180]	164 [156–175]
Rotational								
No. [−]	4.0 [1.8–7.0]	0.0 [0.0–1.0]	0.0 [0.0–1.3]	0.0 [0.0–1.0]	0.0 [0.0–1.0]	1.0 [0.0–1.3]	1.0 [0.5–1.5]	0.0 [0.0–1.0]
Duration [s] *	0.47 [0.43–0.59]	0.64 [0.49–0.74]	0.45 [0.43–0.50]	0.48 [0.44–0.57]	0.57 [0.39–1.17]	0.48 [0.43–0.57]	0.46 [0.43–0.57]	0.44 [0.42–0.56]
RAAPCL [ms]	168 [152–184]	178 [173–229]	166 [151–176]	168 [150–181]	187 [148–269]	166 [151–179]	165 [149–175]	164 [160–205]

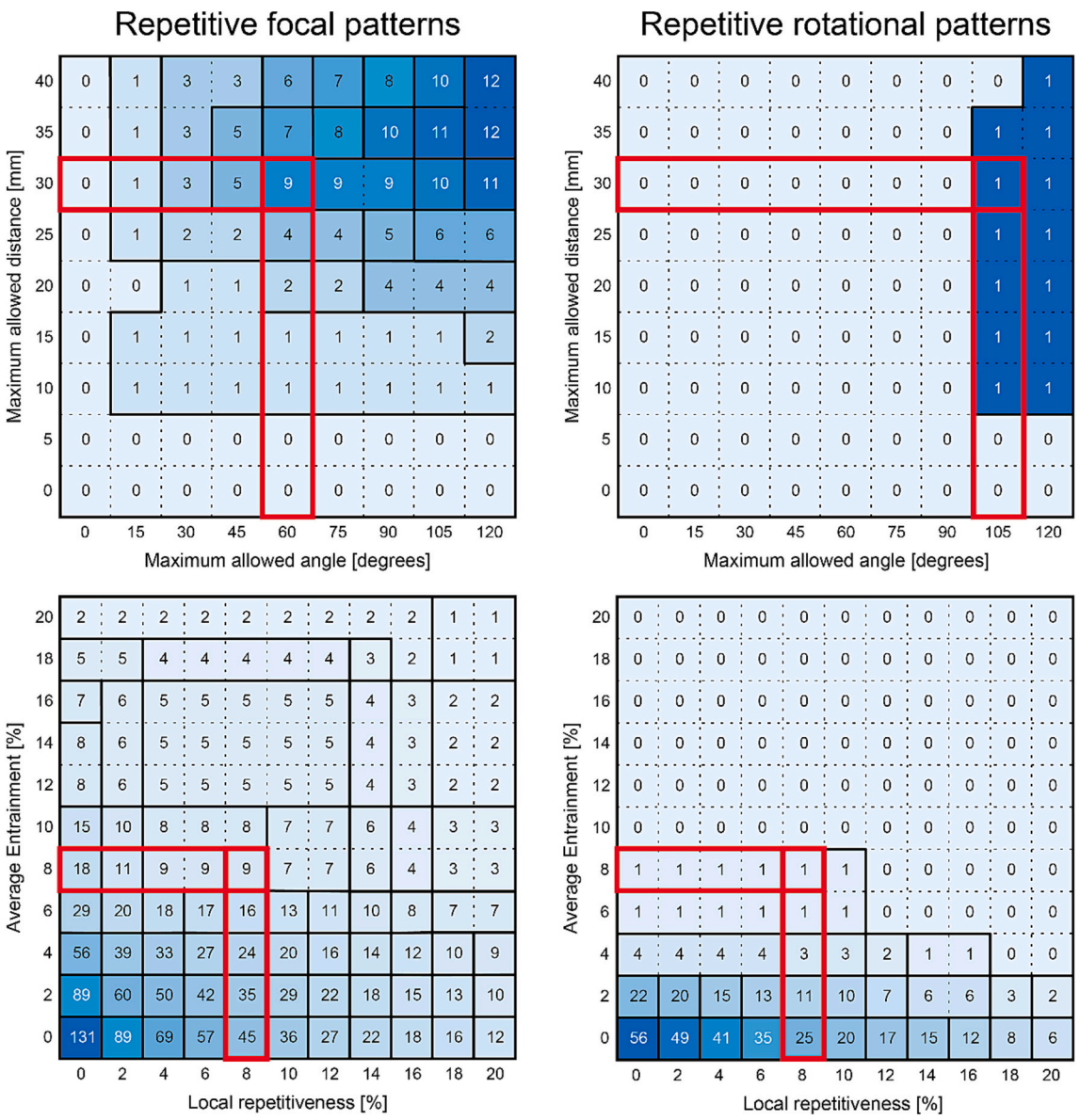

Fig. 2. Sensitivity analyses. (Upper) A heatmap of the most probable sources for different values of the maximum allowed distance and angles (β). The selection of these parameters determined the value of vicinity entrainment by adjusting adjacent recordings and the directionally coherent RAAPs. We applied a hypothetical 5 % threshold for local repetitiveness and vicinity entrainment and counted resulting probable sources detections. The parameters were chosen as 30 mm and 60 degrees for focal activities and 30 mm and 105 degrees for rotational patterns (Lower) A heatmap of the most probable sources detections with varying repetitiveness threshold values. For the 90th percentile threshold we selected, 10 probable sources (9 focal and 1 rotational) were detected.

degrees for the rotational activation patterns. This configuration was necessary because the vicinity of rotational activation patterns can still show a circular activation pattern around the source, resulting in a larger β.

3.3. Most probable sources

Fig. 3 shows the local repetitiveness (horizontal axis) and average entrainment (vertical axis) of all repetitive focal (left) and rotational activation patterns (right). Different colors indicate different patients. When applying a 90th percentile threshold to both the local repetitiveness and average entrainment, 10 (9 focal and 1 rotational from 7 patients) of all 187 source-like activation patterns (5 %) are found to be able to entrain its vicinity and thereby have a higher probability of being a source. In 6 patients (46 %), no entrainment was detected. The location, duration and RAAPCL of only the probable sources are shown in Table 2. Most of the probable sources were located in the SRA or LPV regions (Table 2). The entrainment in the LPV showed significantly shorter duration than their counterparts in SRA (2.6 [2.4–3.1] seconds versus 6.4 [5.2–9.0] seconds, $p = 0.038$). There were no significant differences between RAAPCLs and the number probable sources per patient. An example of a repetitive focal activation pattern and the directional coherent RAAPs in its vicinity is shown in Fig. 4.

Fig. 5 shows the RAAPCL distribution of all focal and rotational activation patterns for each patient. Focal activation patterns are represented as circles and rotational activation patterns as crosses. Probable sources are highlighted in red. The figure illustrates that, with the exception of one patient, probable sources do not possess the shortest RAAPCL within one patient.

4. Discussion

In this study, we present a novel technique that can be used to select the repetitive focal or rotational activation pattern with the highest

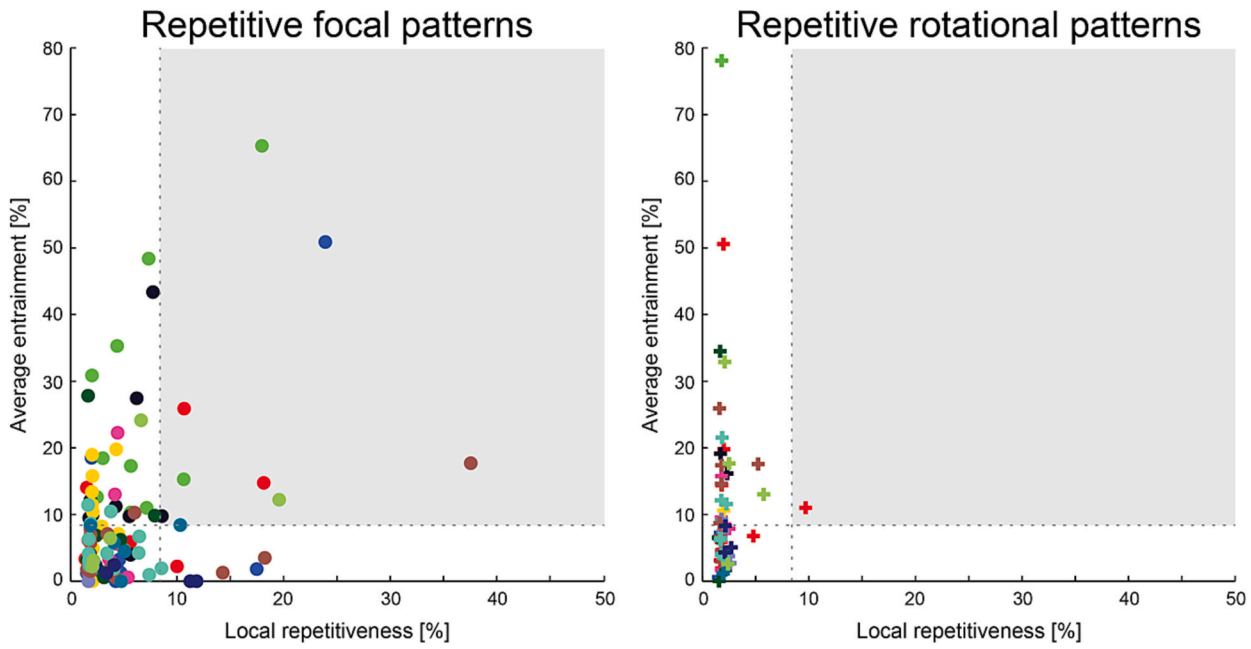

Fig. 3. Local repetitiveness versus average entrainment for repetitive focal (left) and rotational (right) activation patterns for all patients. Each color represents an individual patient. The most probable sources were defined as those located in the plane's upper right corner (gray zone). A 90-percentile threshold on local repetitiveness was used to define this zone.

Table 2
Distribution of probable sources in different regions among patients Data represented as median with [interquartile range]. No., number; RAAPCL, repetitive activation pattern cycle length; s, seconds; ms, milliseconds; SRA, superior right atrium; LPV, left pulmonary veins; RPV, right pulmonary veins. * indicates a significant difference between regions with $p < 0.05$.

	Total	SRA	IRA	Septum
All				
No. [−]**	1.0 [0.0–1.0]	0.0 [0.0–0.3]	0.0 [0.0–1.0]	0.0 [0.0–0.8]
Duration [s]	3.44 [2.52–4.78]	6.40 [5.19–8.95]	2.57 [2.48–2.70]	4.18 [4.18–4.18]
RAAPCL [ms]	164 [135–180]	167 [148–193]	148 [135–180]	175 [175–175]
Focal				
No. [−]**	1.0 [0.0–1.0]	0.00 [0.0–0.3]	0.0 [0.0–1.0]	0.0 [0.0–0.8]
Duration [s]	4.18 [2.59–5.19]	6.4 [5.19–8.95]	2.62 [2.38–3.13]	4.18 [4.18–4.18]
RAAPCL [ms]*	167 [140–185]	167 [148–193]	161 [135–185]	175 [175–175]
Rotational				
No. [−]	0.5 [0.0–1.0]	NA	0.5 [0.0–1.0]	NA
Duration [s]*	2.52 [2.52–2.52]	NA	2.52 [2.52–2.52]	NA
RAAPCL [ms]	132 [132−132]	NA	132 [132–132]	NA

probability of being a source of AF. We achieve this by analyzing their local repetitiveness and their ability to entrain nearby areas in sequential recordings. We propose that highly repetitive focal or rotational activation patterns with highly repetitive directionally coherent activation patterns in its vicinity are likely to be a source. Interestingly, in half of the patients within our retrospective dataset, we found repetitive focal activation patterns with a high probability of being a source. This observation might explain the relatively high AF recurrence rate following routine PVI in patients with persistent AF since these sites are not targeted in a routine PVI. Furthermore, our findings revealed that the most probable sources were not necessarily associated with the shortest RAAPCL, indicating that our approach provides additional insights beyond conventional source detection methods based on dominant frequency or AFCL.

4.1. *Repetitive activation patterns during AF*

RAAPs have been observed during AF in various studies involving both animals and humans [11,13–17]. In previous work by our group, we observed that the majority of RAAPs detected through recurrence plots were peripheral waves [13]. While the CARTOFINDER algorithm does not consider peripheral waves, we propose that repetitive peripheral waves could be indicative of a nearby driver and should not be disregarded.

Furthermore, it has been shown that peripheral RAAPs are reproducible over time by mapping the same anatomical location twice in persistent AF patients, revealing similar peripheral RAAPs during both recordings [18]. A possible explanation for this reproducibility is that this region is entrained by a nearby source. This aligns with an observation by Kawaji et al., who showed that repetitive focal activation patterns, as indicated by CARTOFINDER, re-occur at specific locations before and after PVI [19].

4.2. *Alignment with previous literature*

Our results show that, on average, focal activation patterns were more repetitive than rotational activation patterns and were detected more frequently. These results are in line with the results of others. First of all, the initial analysis of this dataset by Wolf et al. reported similar numbers of focal (7.4 ± 4.4) and rotational (2.4 ± 2.4) activation patterns when using the original CARTOFINDER algorithm [9]. The distribution of these patterns were also similar with the most focal sources in the LPV and SRA. Furthermore, Honarbakhsh et al. also found focal activation patterns to be more repetitive and occur more frequently compared to rotational activation patterns in two studies [3,6]. Whether rotational activation patterns are truly less repetitive and occur less

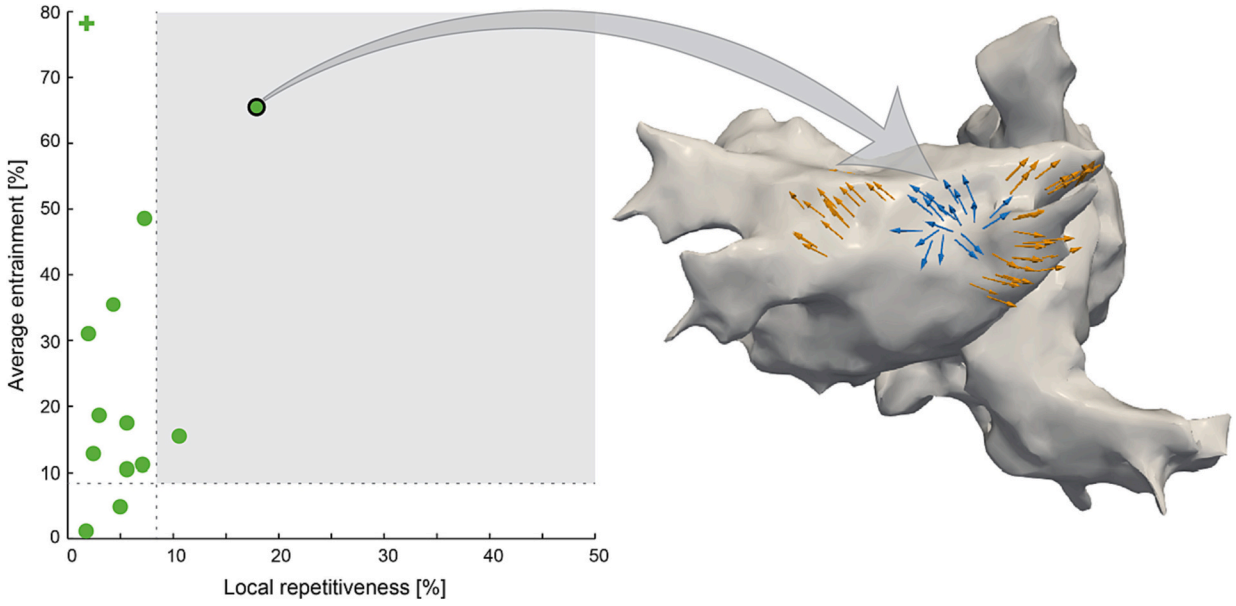

Fig. 4. Example of a probable source. The scatterplot (left) shows all repetitive focal and rotational activation patterns detected in this example patient. The preferential conduction directions of the highlighted site are shown in blue in the poster-anterior view of the atria (right). The directional coherent repetitive activation patterns in the vicinity are shown in orange. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

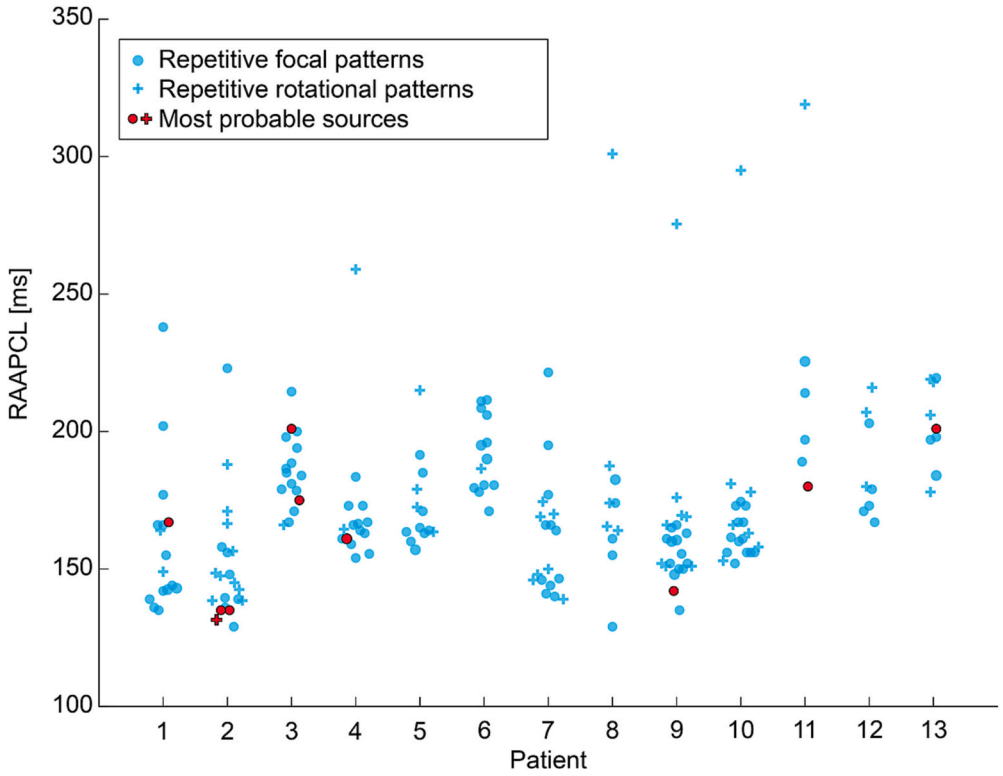

Fig. 5. Repetitive activation pattern cycle lengths (RAAPCL) of all repetitive focal (o) and rotational (+) activation patterns (blue). The most probable sources are highlighted in (red) for each patient. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

frequently or are harder to detect remains unknown. It is known that rotational activation patterns often occupy a large area, making them difficult to map accurately using a mapping catheter with limited spatial coverage. Additionally, reentries are known to lack spatial stationarity, further complicating their detection and quantification [20].

The focal or rotational activation patterns with the highest probability of being a source, according to our technique, are not necessarily the ones with the shortest cycle length. This is supported by Honarbakhsh's observation that sites of sources (confirmed by an effect after a targeted ablation) correlated less frequently to sites of the shortest cycle length and highest dominant frequency than sites with a high organization (low cycle length variation and high regularity index)

[6]. This implies that sources are more closely associated with spatio-temporal organization rather than faster activation sequences.

Focal and rotational activation patterns were present in all anatomical regions, with predilection sites being LPV and SRA areas. This aligns with previous findings reporting a similar spatial distribution of drivers, with a preference for the larger area of the LPV and SRA regions [21].

4.3. Study limitations and future directions

To establish the validity of our technique, further prospective studies are warranted. We have applied an arbitrary 90th percentile threshold for repetitiveness to detect probable sources. Whether a single repetitiveness threshold can be universally employed for all patients remains uncertain. Nevertheless, the plot presented in the example (Fig. 4) could serve as a valuable tool for a patient-specific investigation without the need for a fixed threshold. This plot indeed effectively displays the repetitive activation patterns that are most likely to entrain their vicinity and, thereby, are most likely to be considered a source.

Furthermore, the retrospective design of our current study hinders us from validating whether the probable sources, as detected by our technique are associated with relevant mechanisms of AF maintenance since the effect of a targeted ablation of these sites remains unknown. A prospective observational study could offer the first indirect validation of the proposed technique. For example, by examining the correlation between the presence of highly probable sources outside the PVs, as detected by our approach, and post-PVI AF recurrences. However, definitive confirmation of our technique's validity would require direct evidence obtained by performing targeted ablations guided this same technique.

The primary limitation of our algorithm is the absence of direct evidence establishing a causal link between the repetitive focal or rotational activation patterns and the directionally coherent RAAPs in neighboring recordings. However, in clinical settings, electrophysiologists have the opportunity to remap regions indicated by our algorithm to confirm this causality before targeting a site.

In addition to the lack of causality, there are technical challenges associated with densely mapping the entire atria within a reasonable procedural timeframe. Furthermore, issues like poor electrode contact and electrogram fractionation are commonly encountered during endocardial mapping and may potentially affect the accuracy of our framework for local activation time annotation and RAAP detection. It is essential to address these challenges in future research to enhance the robustness and applicability of our approach.

The current study was limited to using the Pentaray catheter while other high-density contact mapping catheters are available (e.g. HDgrid, Octaray, and Optrell). These catheters differ from each other in terms of spatial coverage, electrode density, and distribution. Since radial spread of activation, rotational activities, and conduction direction estimations can be achieved in each of these catheters, our methodology is applicable to other high-density mapping catheters. Some other catheters may even provide additional benefits due to characteristics of these catheters. For instance, HDgrid and Optrell have a uniform electrode arrangement that may enhance the estimation of conduction direction. OctaRay, on the other hand, includes more electrodes than PentaRay and therefore might more accurately detect radial spread of activation and rotational activities.

5. Conclusion

In this study, we introduce a new method that can be used to select the repetitive focal or rotational activation pattern with the highest probability of being a source of AF. This technique involves measuring the local repetitiveness of an activation pattern and its ability to entrain its vicinity. We propose that sites showing high repetitive focal or rotational activation patterns, accompanied by nearby repetitive RAAP in the same direction as the source, are more likely to be sources capable of entraining and thereby driving AF.

Funding

This work was supported by the Netherlands Heart Foundation (CVON2014-09, RACE V Reappraisal of Atrial Fibrillation: Interaction between hyperCoagulability, Electrical remodeling, and Vascular Destabilisation in the Progression of AF, and Grant number 01-002-2022-0118, EmbRACE: Electro-Molecular Basis and the theRapeutic management of Atrial Cardiomyopathy, fibrillation and associated outcomEs), the European Union (ITN Network Personalize AF: Personalized Therapies for Atrial Fibrillation: a translational network, grant number 860974; MAESTRIA: Machine Learning Artificial Intelligence Early Detection Stroke Atrial Fibrillation, grant number 965286; REPAIR: Restoring cardiac mechanical function by polymeric artificial muscular tissue, grant number 952166).

CRediT authorship contribution statement

Ben J.M. Hermans: Conceptualization, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Ozan Özgül:** Conceptualization, Formal analysis, Investigation, Methodology, Software, Validation, Writing – original draft, Writing – review & editing. **Michael Wolf:** Data curation, Formal analysis, Resources, Writing – review & editing. **Victor G. Marques:** Conceptualization, Software, Writing – review & editing. **Arne van Hunnik:** Conceptualization, Methodology, Writing – review & editing. **Sander Verheule:** Conceptualization, Methodology, Writing – review & editing. **Sevasti-Maria Chaldoupi:** Conceptualization, Methodology, Writing – review & editing. **Dominik Linz:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Milad El Haddad:** Conceptualization, Formal analysis, Methodology, Writing – review & editing. **Mattias Duytschaever:** Conceptualization, Data curation, Formal analysis, Resources, Supervision, Writing – review & editing. **Pietro Bonizzi:** Conceptualization, Methodology, Software, Supervision, Writing – review & editing. **Kevin Vernooy:** Conceptualization, Methodology, Writing – review & editing. **Sébastien Knecht:** Data curation, Supervision, Writing – review & editing. **Stef Zeemering:** Conceptualization, Formal analysis, Methodology, Software, Supervision, Writing – review & editing. **Ulrich Schotten:** Conceptualization, Funding acquisition, Investigation, Methodology, Resources, Software, Supervision, Writing – review & editing.

Declaration of competing interest

US received consultancy fees or honoraria from Università della Svizzera Italiana (USI, Switzerland), Roche Diagnostics (Switzerland), EP Solutions Inc. (Switzerland), Johnson & Johnson Medical Limited, (United Kingdom), Bayer Healthcare (Germany). US is co-founder and shareholder of YourRhythmics BV, a spin-off company of the University Maastricht.

References

[1] Inoue K, Hikoso S, Masuda M, Furukawa Y, Hirata A, Egami Y, et al. Pulmonary vein isolation alone vs. more extensive ablation with defragmentation and linear ablation of persistent atrial fibrillation: the EARNEST-PVI trial. EP Europace 2021; 23:565–74. https://doi.org/10.1093/europace/euaa293.

[2] Daoud EG, Zeidan Z, Hummel JD, Weiss R, Houmsse M, Augostini R, et al. Identification of repetitive activation patterns using novel computational analysis of multielectrode recordings during atrial fibrillation and flutter in humansvol. 3. JACC: Clinical Electrophysiology; 2017. p. 207–16. https://doi.org/10.1016/j.jacep.2016.08.001.

[3] Honarbakhsh S, Schilling RJ, Providencia R, Keating E, Sporton S, Lowe M, et al. Automated detection of repetitive focal activations in persistent atrial fibrillation: validation of a novel detection algorithm and application through panoramic and sequential mapping: HONARBAKHSH et al. J Cardiovasc Electrophysiol 2019;30: 58–66. https://doi.org/10.1111/jce.13752.

[4] Calvo D, Rubín J, Pérez D, Morís C. Ablation of rotor domains effectively modulates dynamics of human: long-standing persistent atrial fibrillation, Circ. Arrhythmia and Electrophysiology 2017;10:e005740. https://doi.org/10.1161/CIRCEP.117.005740.

[5] Honarbakhsh S, Schilling RJ, Dhillon G, Ullah W, Keating E, Providencia R, et al. A Novel Mapping System for Panoramic Mapping of the Left Atrium, JACC: Clinical Electrophysiology 2018;4:124–34. https://doi.org/10.1016/j.jacep.2017.09.177.

[6] Honarbakhsh S, Schilling RJ, Providencia R, Keating E, Chow A, Sporton S, et al. Characterization of drivers maintaining atrial fibrillation: correlation with markers of rapidity and organization on spectral analysis. Heart Rhythm 2018;15:1296–303. https://doi.org/10.1016/j.hrthm.2018.04.020.

[7] G. Hindricks, T. Potpara, N. Dagres, E. Arbelo, J.J. Bax, C. Blomström-Lundqvist, G. Boriani, M. Castella, G.-A. Dan, P.E. Dilaveris, L. Fauchier, G. Filippatos, J.M. Kalman, M. La Meir, D.A. Lane, J.-P. Lebeau, M. Lettino, G.Y.H. Lip, F.J. Pinto, G.N. Thomas, M. Valgimigli, I.C. Van Gelder, B.P. Van Putte, C.L. Watkins, ESC Scientific Document Group, P. Kirchhof, M. Kühne, V. Aboyans, A. Ahlsson, P. Balsam, J. Bauersachs, S. Benussi, A. Brandes, F. Braunschweig, A.J. Camm, D. Capodanno, B. Casadei, D. Conen, H.J.G.M. Crijns, V. Delgado, D. Dobrev, H. Drexel, L. Eckardt, D. Fitzsimons, T. Folliguet, C.P. Gale, B. Gorenek, K.G. Haeusler, H. Heidbuchel, B. Iung, H.A. Katus, D. Kotecha, U. Landmesser, C. Leclercq, B.S. Lewis, J. Mascherbauer, J.L. Merino, B. Merkely, L. Mont, C. Mueller, K.V. Nagy, J. Oldgren, N. Pavlović, R.F.E. Pedretti, S.E. Petersen, J.P. Piccini, B.A. Popescu, H. Pürerfellner, D.J. Richter, M. Roffi, A. Rubboli, D. Scherr, R.B. Schnabel, I.A. Simpson, E. Shlyakhto, M.F. Sinner, J. Steffel, M. Sousa-Uva, P. Suwalski, M. Svetlosak, R.M. Touyz, N. Dagres, E. Arbelo, J.J. Bax, C. Blomström-Lundqvist, G. Boriani, M. Castella, G.-A. Dan, P.E. Dilaveris, L. Fauchier, G. Filippatos, J.M. Kalman, M. La Meir, D.A. Lane, J.-P. Lebeau, M. Lettino, G.Y.H. Lip, F.J. Pinto, G. Neil Thomas, M. Valgimigli, I.C. Van Gelder, C.L. Watkins, T. Delassi, H.S. Sisakian, D. Scherr, A. Chasnoits, M.D. Pauw, E. Smajić, T. Shalganov, P. Avraamides, J. Kautzner, C. Gerdes, A.A. Alaziz, P. Kampus, P. Raatikainen, S. Boveda, G. Papiashvili, L. Eckardt, V. Vassilikos, Z. Csanádi, D.O. Arnar, J. Galvin, A. Barsheshet, P. Caldarola, A. Rakisheva, I. Bytyçi, A. Kerimkulova, O. Kalejs, M. Njeim, A. Puodziukynas, L. Groben, M.A. Sammut, A. Grosu, A. Boskovic, A. Moustaghfir, N. de Groot, L. Poposka, O.-G. Anfinsen, P.P. Mitkowski, D.M. Cavaco, C. Siliste, E.N. Mikhaylov, L. Bertelli, D. Kojic, R. Hatala, Z. Fras, F. Arribas, T. Juhlin, C. Sticherling, L. Abid, I. Atar, O. Sychov, M.G.D. Bates, N.U. Zakirov. ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2020;42(2021):373–498. https://doi.org/10.1093/eurheartj/ehaa612.

[8] Quintanilla JG, Shpun S, Jalife J, Filgueiras-Rama D. Novel approaches to mechanism-based atrial fibrillation ablation. Cardiovasc Res 2021;117:1662–81. https://doi.org/10.1093/cvr/cvab108.

[9] Wolf M, Tavernier R, Zeidan Z, El Haddad M, Vandekerckhove Y, Pooter JD, et al. Identification of repetitive atrial activation patterns in persistent atrial fibrillation by direct contact high-density electrogram mapping. J Cardiovasc Electrophysiol 2019;30:2704–12. https://doi.org/10.1111/jce.14214.

[10] Zeemering S, Maesen B, Nijs J, Lau DH, Granier M, Verheule S, et al. Automated quantification of atrial fibrillation complexity by probabilistic electrogram analysis and fibrillation wave reconstruction. Annu Int Conf IEEE Eng Med Biol Soc 2012;2012:6357–60. https://doi.org/10.1109/EMBC.2012.6347448.

[11] Zeemering S, van Hunnik A, van Rosmalen F, Bonizzi P, Scaf B, Delhaas T, et al. A novel tool for the identification and characterization of repetitive patterns in high-density contact mapping of atrial fibrillation. Front Physiol 2020;11. https://doi.org/10.3389/fphys.2020.570118 (accessed December 28, 2022).

[12] Verma B, Oesterlein T, Loewe A, Luik A, Schmitt C, Dössel O. Regional conduction velocity calculation from clinical multichannel electrograms in human atria. Comput Biol Med 2018;92:188–96. https://doi.org/10.1016/j.compbiomed.2017.11.017.

[13] van Rosmalen F, Maesen B, van Hunnik A, Hermans BJM, Bonizzi P, Bidar E, et al. Incidence, prevalence, and trajectories of repetitive conduction patterns in human atrial fibrillation. EP Europace. 2021;23:i123–32. https://doi.org/10.1093/europace/euaa403.

[14] van Hunnik A, Zeemering S, Podziemski P, Simons J, Gatta G, Hannink L, et al. Stationary atrial fibrillation properties in the goat do not entail stable or recurrent conduction patterns. Front Physiol 2018;9:947. https://doi.org/10.3389/fphys.2018.00947.

[15] Ng J, Gordon D, Passman RS, Knight BP, Arora R, Goldberger JJ. Electrogram morphology recurrence patterns during atrial fibrillation. Heart Rhythm 2014;11:2027–34. https://doi.org/10.1016/j.hrthm.2014.08.002.

[16] Zaatari G, Mitrani R, Bohorquez J, Ng J, Ng J, Rivner H, et al. Electrogram morphology recurrence for mapping persistent atrial fibrillation. JACC: Clinical Electrophysiology 2023;9:526–40. https://doi.org/10.1016/j.jacep.2022.11.003.

[17] P. Ganesan, B. Deb, R. Feng, M. Rodrigo, S. Ruiperez-Campillo, A.J. Rogers, P. Clopton, P.J. Wang, S. Zeemering, U. Schotten, W.-J. Rappel, S.M. Narayan, Quantifying a spectrum of clinical response in atrial tachyarrhythmias using spatiotemporal synchronization of electrograms, EP Europace. (2023) euad055. doi:https://doi.org/10.1093/europace/euad055.

[18] Mann I, Linton NWF, Coyle C, Howard JP, Fudge M, Lim E, et al. RETRO-MAPPING: a new approach to activation mapping in persistent atrial. Fibrillation Reveals Evidence of Spatiotemporal Stability, Circ: Arrhythmia and Electrophysiology 2021;14:e009602. https://doi.org/10.1161/CIRCEP.121.009602.

[19] Kawaji T, Aizawa T, Hojo S, Yaku H, Nakatsuma K, Kaneda K, et al. Reproducibility and stability of atrial fibrillation drivers identified by an automated algorithm: CARTOFINDER. J Interv Card Electrophysiol 2022;65:461–70. https://doi.org/10.1007/s10840-022-01254-5.

[20] Nattel S. Molecular and Cellular Mechanisms of Atrial Fibrosis in Atrial Fibrillation, JACC: Clinical Electrophysiology 2017;3:425–35. https://doi.org/10.1016/j.jacep.2017.03.002.

[21] Unland R, Bergau L, El Hamriti M, Guckel D, Piran M, Fink T, et al. Find me if you can: first clinical experience using the novel CARTOFINDER algorithm in a routine workflow for atrial fibrillation ablation. JCM 2021;10:2979. https://doi.org/10.3390/jcm10132979.