Characterization of temporal electrical activity patterns for detection of critical isthmus regions of recurrent atypical atrial flutter

N. Vonderlin[1,2], J. Siebermair[1,2], E. Pesch[1], M. Koehler[1], L. Riesinger[1,2], E. Kaya[1], S. Kochhaeuser[1], R.A. Janosi[1], T. Rassaf[1], R. Wakili[1,2]

[1] Department of Cardiology and Vascular Medicine, West-German Heart and Vascular Center Essen, University of Essen Medical School, University Duisburg-Essen, Essen, Germany

[2] German Centre for Cardiovascular Research (DZHK)

Short title: Role of Lumipoint® in atypical atrial flutter

Key Words: Lumipoint®, isthmus, reentry, atypical atrial flutter

Correspondence

Reza Wakili, MD (reza.wakili@uk-essen.de)

Department of Cardiology and Vascular Medicine

West German Heart and Vascular Center Essen

University Hospital Essen

University Duisburg-Essen, Essen

Hufelandstrasse 55, 45147 Essen, Germany

Phone: +49 201 / 723 - 84882

Fax: + 49 201 / 723 - 5404

Conflict of interest: Reza Wakili has received consultant fees, speaking honoraria and travel expenses from Biotronik; investigator-initiated funding for research projects (initiated by him). Other authors: No conflicts of interest.

Funding: (None)

Introduction

Identifying the critical isthmus region (CIR) of complex atrial tachycardias (AT) is challenging. The Lumipoint® (LP) software, developed for the Rhythmia® mapping system, aims to facilitate successful termination of ATs by identifying the CIR.

Objective

Objective of this study was to evaluate specificity and sensitivity of LP regarding arrhythmia-relevant CIR detection in patients with atypical-atrial-flutter (AAF).

Methods

In this retrospective analysis we analyzed 57 AAF-forms. Electrical activity (EA) was mapped over tachycardia cycle length resulting in a 2-dimensional EA pattern. The hypothesis was that an EA minimum suggests a potential CIR with slow-conduction-zone.

Results

A total of n=33 patients were included. LP-algorithm identified a mean of 2.4 EA minima and 4.4 suggested CIRs per AAF-form. Overall, we observed a low specificity with 12.3% but a high sensitivity of 98.2%. Detailed EA analysis revealed that depth (≤20%) and width (>50ms) of EA minima were the best predictors of relevant CIRs. Wide minima occurred rarely (17.5%), while low minima were more frequently present (75.4%). Minima with a depth of EA≤20% showed the best sensitivity and specificity overall (95% and 60%, respectively). Analysis in recurrent ablations in 5 patients presenting de-novo AAF revealed that the CIR of de-novo AAF was already detected by LP during the index procedure.

Conclusion

The LP algorithm provides an excellent sensitivity (98.2%), but poor specificity (12.3%) to detect the CIR in AAF. Specificity improved by preselection of the lowest and widest EA minima. In addition, there might be role of initial bystander CIRs becoming relevant for future AAFs.

Introduction

Atrial scar regions favor the formation of slow conducting areas in the myocardial chambers and thereby contribute to the occurrence of reentry-tachycardias, e.g., atypical atrial flutter (AAF). This is frequently observed in pre-ablated patients, especially after pulmonary veins isolation (PVI). Studies show that over 30% of patients develop clinically relevant atrial tachycardia (AT) during follow-up (FU) [1]. Ablation of those ATs is often difficult due to different substrates, variability of cycle length (CL), varying forms of atrial flutter and different locations in the atrium [2-5]. Essential for the successful treatment of the reentry-tachycardia is the identification of the underlying mechanism. The critical isthmus region (CIR) usually corresponds to a slow conduction zone building the pathophysiological basis for electrical re-entry [6]. Because of slow conduction in a localized area of cardiac tissue, a low cumulative electrical activity (EA) of cardiomyocytes over time is resulting in low amplitude intracardiac electrograms (EGMs). Hence, regions with low EA over time are suspected to represent slow conduction areas due to diseased tissue or remodeling, e.g. fibrosis. Translating this hypothesis to a surface ECG isoelectric phases of the ECG between p-waves are suspected to represent the time of electrical slow conduction through the CIR [7]. Since these CIR are crucial for tachycardia initiation and maintenance, the identification and ablation of the CIR is the aim of electrophysiological studies targeting reentry tachycardias.

Lumipoint® (LP) is a novel software algorithm, developed for the Rhythmia® mapping software, which aims to identify the CIR of reentrant tachycardias by applying the theory of low EA representing potential CIRs [8, 9]. The feature detects the temporal distribution of the mapped electrical activation by analysis of all single EGM to determine activity at each location dependent of local activation time.

The tool ‘skyline’ generates a 2-dimensional histogram in which a full chamber activation is displayed (see figure 1A, red box). It can be used to highlight regions of interest on the map that activate within a certain time within the cycle [8]. Peaks in the histogram correspond to areas with high cumulative EA while a valley is seen as very low EA surface activation. The latter is the point of interest cause areas of minimal activation may correspond to slow conduction zones and therefore to the potential CIR of the AAF.

To evaluate if the new algorithm LP improve the interpretation of complex atrial macro-reentry tachycardia and identifying potential ablation strategies, we performed this

retrospective study. The objective was to determine the sensitivity and specificity of the algorithm for determining the CIR of reentrant AAF tachycardias. Furthermore, we sought to investigate if LP can predict relevant CIR for future clinically relevant ATs.

Methods

Study population

In this is a retrospective, single center study; in total n=33 patients were included, who underwent ablation by ultra-high-density mapping guided AT-ablation with the Rhythmia® mapping system in our center from 11/2017 to 09/2019. The mean follow-up time was 10±7 months. All patients gave written informed consent before ablation. The methods were carried out in accordance with the relevant guidelines and regulations of the University of Duisburg-Essen. The protocol was approved by the institutional review board and the local ethics committee (registration number: 19-8714-BO).

Electrophysiological study and mapping

Antiarrhythmic drugs, if administered, were continued during study period. All patients were on oral anticoagulation therapy at least >24 hours before catheter ablation date. Atrial thrombus was excluded by transesophageal echocardiography in every patient <3 days before the procedure. Throughout the procedure, an activated clotting time of >300 seconds was aimed for.

During procedure, a steerable decapolar catheter was placed in coronary sinus (CS). We used the Orion™ multipolar basket catheter and Rhythmia™ system (both Boston Scientific, Marlborough, MA) for the mapping of AAF. A local activation (LAT) map was generated with automatic standard beat acceptance criteria based on the annotations-algorithm: (1) cycle length (CL) variation, (2) activation time difference variations between the CS EGMs, (3) propagation reference (ΔR), (4) respiration, (5) QRS morphology “favorite beat” (ECG), (6) mapping catheter movement, (7) electrogram stability compared to last beat, (8) tracking quality and (9) window. Entrainment mapping was not performed.

Ablation approach

Based on the atrial local activation (LAT) map, the most likely dominant AAF mechanism and identification of the circuit was determined. Appropriate ablation sites

were selected in dependence of the anatomic distance, catheter stability, tissue thickness and vulnerable structures located nearby. Mostly, the selected ablation side was a narrow scope between scars and anatomical obstacles. In theory, several ablation sites can lead to the termination of the AAF, practical ablation site was chosen by the discretion of the operator. Independent of the selected isthmus, the aim of ablation was an ablation line resulting in a bidirectional block [10-12]. Pulmonary vein isolation (PVI) was obtained in the same procedure if needed. We used a 3.5 mm tip ablation catheter (Thermocool®; Biosense Surround Flow, Biosense Webster, Diamond Bar, CA) to generate radiofrequency energy with maximal 35 W (30W at the posterior wall). Each RF ablation was limited to 240 seconds, delivered by a 500 kHz ablation unit (Stockert EP shuttle; Biosense Webster, Inc, Baldwin Park, CA).

LUMIPOINT® algorithm

In our study we applied the LP algorithm retrospectively. LP offers the possibility to apply three different tools 'skyline', fractioned electrocardiograms and double potentials. In our study we focused on the first tool 'skyline' which creates a 2D Map of electrical activity over the CL of the tachycardia. Thereby, the tool uses the information of full chamber surface activation. The result is the 'skyline' which plots the relative proportion of the atrial surface area that is activated in time throughout the entire CL (figure 1A). The result is a normalized global activation histogram which values ranging from 0.01-1.0 (for our calculations 1-100%). 'Peaks' correspond with points of maximal electrical activation when a large part of the atrium is being activated and were called maximum in our analyses. The points of interest are the 'valleys' or "minima" of electrical activity (figure 1B), which represent potentially the CIR as surrogate of a slow conduction [9, 13].

In our study, we analyzed the 'skyline' pattern as follows: a minimum was accepted if the selected EA's relative value it is <50% and peaks before and after has to be at least of ≥5% higher than the minimum of interest. Further additional minima were included if they EA value did not exceed the lowest minimal EA point more than 2-fold (figure 1C).

By starting the 'activation search' feature of LP, a predefined unit time of 30 ms (green line) runs over the electrical activation map. At every moment, the activated areas are highlighted at the atrium surface. When the green line reaches a predefined, potential 'isthmus' – regions with minimal cumulative EA over the CL of the tachycardia – were

highlighted. A minimum could contain several highlighted areas and therefore several isthmi (e.g. see figure 1B: 1 minimum with 2 isthmi). The definition of CIR was based on the assumption that an ablation would lead to the termination of AAF, always re-evaluated by a successful termination under ablation confirming the correct initial suspected re-entry mechanism.

Further we analyzed the width and depth of EA minima in detail and categorized the in 5 groups with respect to depth (0-10%, >10-20%, >20-30%, >30-40% and >40-50% of EA) and 7 groups according to width (0-10ms, >10-20ns, >20-30ms, >30-40ms, >40-50ms, >50-100ms and >100-160ms).

Study endpoints

Primary study endpoint was to evaluate the quality of the selection of proposed isthmi by the LP algorithm. We aimed for determining the sensitivity and specificity for the CIR as well as possibilities to improve the algorithm by further characterization of minima.

Secondary endpoints comprised the analysis of total number of detected isthmus, as well as their number per AFF and minimum. Furthermore, we evaluated the recurrence rate of AAF during FU, the number of patients who underwent re-ablation and if potential LP suggested CIR regions during index procedure were involved in future recurrent clinical ATs in the individual patient.

Statistical analysis

Data in our study are expressed as mean (±standard deviation) for continuous variables or as numbers and percentages for categorical variables. For categorical variables, Chi-square analysis or Fisher's exact test were applied. Statistically significance was considered by a p-value <0.05.

Results

The analysis of the included 33 patients revealed a mean number of 1.7 AAF forms per patient. In total we analyzed 57 atrial macro-reentry tachycardia forms. Out of these n=49 AAF were localized in left atrium and n=8 in right atrium, but not involving the tricuspid isthmus. In all cases targeted ablation AAFs lead to successful termination or conversion into another AAF form.

Patient characteristics

The baseline characteristics of the 33 patients are listed in table 1. Mean age was 70.6 years, more than half of patients were male (54.5%). Echocardiographic examination revealed a preserved ejection fraction of left ventricle. Most of patients (90.9%) were treated with at least one antiarrhythmic drug (AAD); in most cases betablockers (90.9%), followed by amiodarone and flecainide (24.2% and 9.1%, respectively). The most common cardiovascular risk factor was arterial hypertension (84.8%). Almost 9% suffered from a stroke or TIA in the past and 45.5% had a diagnosis of coronary artery disease (CAD). In addition, 45.5% of patients were equipped with a cardiac device (pacemaker, ICD or CRT-D/P). Most patients (84.8%) had a previous history of cardiac intervention. In most cases patients were pre-ablated in past (69.7%), thereof about half of patients did undergo a PVI before (51.5% of total). A history of prior cardiac surgery was the case in 24.2%, and of a transcatheter mitral valve repair or valvuloplasty in 9.1%.

Electrophysiological characteristics

Table 2 shows the electrophysiological characteristics and results of the skyline analysis of the mapped AT. Overall, 57 AAFs (1.7 AAF per patient) were analyzed in this retrospective study. The mean cycle length of the AAFs was 291.0 ± 70.2ms. The mean total mapping time was 12.1 ± 7.0 minutes. In total 56/57 (98.2%) AAFs were terminated by ablation, while only one AAF (1.8%) converted in atrial fibrillation (AFib) under ablation.

The skyline analysis revealed a total number of 137 minima, mean number of minima per AAF was 2.4. Figure 2A depicts the detailed numbers and distribution of minima per AAF (1 minimum/AAF: 25%; 2 minima/AAF: 26%; 3 minima/AAF: 39%; 4 minima/AAF: 5%; 5 minima/AAF: 5%). The total number of highlighted areas representing the number of potential isthmi was n=248. LP identified 1.8 isthmi per minimum and 4.4 isthmi per AAF in the whole cohort. Figure 2B shows the distribution of isthmus number per minimum (1 isthmus/minimum: 46%; 2 isthmi/minimum: 32%; 3 isthmi/minimum: 17%; 4 isthmi/minimum: 5%). In addition, figure 2C illustrates the number of isthmi per AAF (1 isthmus/AAF: 12%; 2 isthmi/AAF: 18%; 3: isthmi/AAF: 12%; 4 isthmi/AAF: 16%; 5 isthmi/AAF: 16%, ≥6 isthmi/AAF: 26%).

Sensitivity and specificity on CIR detection

In a next step we evaluated the potential involvement of the LP-suggested isthmi into the re-entry circuit and the opportunity of AAF termination at this region by ablation. Our analysis revealed that 60.9% (151/248) of suggested isthmi were part of the reentry as shown in figure 3A. Analyses of the sensitivity and specificity of the LP algorithm showed a high sensitivity of 98.2% (56/57) with respect to detect at least one CIR of the AAF, but a very low specificity with 12.3% (7/57) for detecting only the relevant CIR, which would correspond to AAF termination site (figure 3B). To further improve the specificity, we analyzed different characteristics of the minima and evaluated if or how applying distinct pre-selection criteria would translate into higher specificity. The mean width of a minimum was 24.5±22 ms, while the mean EA level was obtained at 22.7±13.0%, always related to the maximum level (100%) of the EA in the skyline pattern. The mean peak preceding as well as after a minimum were mostly located between 60-65% of maximum EA (65.2±28.4% and 63.7±27.5%, respectively).

Our analysis revealed that in case we select the widest minimum only (mean 35.9±29.4ms), we had a decrease in sensitivity down to 80.7% (46/57; CIR was involved in longest minima) but an improved specificity of 49.1% (28/57). The best result was yield, when the lowest/ deepest minimum (average 14.4±9.8%) out of all suggested was chosen. In this setting the sensitivity was still high with 91.2% (figure 3C) and the specificity increased up to 49.1% (28/57) when compared to the baseline condition.

In addition, we further characterized the minima regarding its width with respect to predicting the potential CIR. Figure 4A shows, deeper minima are associated with an improved specificity as well as sensitivity in comparison to higher minima (0-10%: sensitivity 91%, specificity 56%; >10-20%: sensitivity 80%, specificity 49%; >20-30%: sensitivity 44%, specificity 13%; >30-40%: sensitivity 50%, specificity 9%; >40-50%: sensitivity 44%, specificity 0%). With regard to the length (figure 4B), longer minima showed better sensitivity as well as specificity in contrast to shorter minima (0-10ms: sensitivity 74%, specificity 16%; >10-20ms: sensitivity 51%, specificity 22%; >20-30ms: sensitivity 66%, specificity 34%; >30-40ms: sensitivity 92%, specificity 33%; >40-50ms: sensitivity 67%, specificity: 33%; 50-100ms: sensitivity 100%, specificity 75%; >100-160ms: sensitivity 100%, specificity 100%). In a next step we analyzed the deepest minima of each AAF (n=57); here we also found an improved sensitivity and

specificity of deeper minima in comparison to higher minima (see figure 4C; 0-10%: sensitivity 93%, specificity 62%; >10-20%: sensitivity 100%, specificity 57%; >20-30%: sensitivity 80%, specificity 20%; >30-40%: sensitivity 67%, specificity 0%; >40-50%: sensitivity 100%, specificity 0%). Taken together, lowest minima characterized by a depth of EA ≤20% (43/57 cases), showed a very good sensitivity as well as specificity (95% and 60% respectively).

Finally, we compared the longest minima of each AAF (see figure 4D). Wide minima were associated with an improved prediction of potential CIR (0-10ms: sensitivity 100%, specificity 0%; >10-20ms: sensitivity 50%, specificity 21%; >20-30ms: sensitivity 89%, specificity 44%; >30-40ms: sensitivity 89%, specificity 44%; >40-50ms: sensitivity 67%, specificity: 33%; 50-100ms: sensitivity 100%, specificity 86%; >100-160ms: sensitivity 100%, specificity 100%). In conclusion, minima longer than 50ms (in 10/57 cases), had an excellent sensitivity with 100% as well as specificity with 90%.

Prediction of other atrial tachycardias

Furthermore, we evaluated if suggested CIRs during the index procedure were involved in future clinical AAFs/ATs. As mentioned above, 60.6% (20/33) patients had a recurrence of an AAF during the follow-up period of 10±7 months (figure 5A). In total 30.3% (n=10) of the patients had a recurrence of AAF, 18.2% (n=6) a recurrence of AFib, and 12.1% (n=4) had recurrence of both, AAF plus AFib. Of the patients with recurrent AAF (n=14), 50% (7/14) underwent re-ablation (figure 5A).

Figure 5B illustrates the results of the association of potential CIRs detected by LP algorithm during the index procedure and their involvement in subsequent AAF. During the index procedure 12/33 patients developed a second flutter form and two patients showed even a third AAF form. In all but only one case, a relevant CIR was detected by the LP algorithm during the mapping of the first clinical AAF form.

Figure 5C illustrates the association of potential CIRs detected during the index procedure and their involvement in recurrent de novo AAF occurring during follow-up. In total n=9 recurrent AAF forms in 7 patients were examined, 4/9 were AAFs were recurrences of the index tachycardia, while 5/9 were new AAF forms. In all cases (5/5) of a novel recurrent AAF a corresponding matching CIR was already identified by the LP algorithm during the index procedure (Figure 5C).

Discussion

Over the last years, important advantages could be achieved by developing new high-density mapping systems improving the treatment options of cardiac arrhythmias [14, 15]. Mapping, facilitated by rapid acquisition of thousands electroanatomic points including activation time, allows the operator a deeper understanding of the arrhythmogenic mechanisms and pathogenesis. Taken the fact that ablation emerged to one of the most frequent used anti-arrhythmogenic therapies, post-ablation tachycardias, mainly comprising complex reentry tachycardias, became much more common [16, 17]. Based on this, there is a clear demand on high-density mapping features to facilitate precise ablation strategies. In this retrospective study, we evaluated the sensitivity and specificity of a recent developed 3D LAT mapping based algorithm for characterization and ablation guidance of complex ATs. We observed that the LP algorithm provides a promising tool for reliably detecting the CIR of a reentrant AAF and might carry the potential for identification of arrhythmogenic substrate regions.

Patient and AAF characteristics

Consistent to the results of previous studies, a history of pre-ablation or cardiac surgery was present in the majority of the studied patients [5, 18-20]. Mean age in our study cohort was 71 years, which is rather old compared to patient cohorts of previous studies [9, 15, 21]. In our study, 1.7 ATs per patients were detected and mapped. This is in line with previous studies, in which 1.3-1.6 AT forms per patient were reported [9, 15, 21, 22]. The mean CL of our macro-reentrant AT was 291 ms, which is also comparable to previous studies (CL range from 275 to 299 ms) [15, 21].

Lumipoint® as a predictor of critical isthmus ablation regions

The ‘skyline’ tool of LP produces a global activation histogram, which shows areas being activated at any given timeframe. Highlighted areas in the activation map, based on the minima of the global activation histogram are strongly related to slow conduction, lines of block or wavefront collision. In our study, 60.9% of all isthmi of all analyzed minima were located within the AAF reentry circuit. These results go along with data of a previous published reports, in which 60-67% of the isthmi were located in the AT reentry [9, 21].

Role of electrical activation minima

To date there are three published studies which investigated the LP 'skyline' tool in patients with ATs [9, 21, 22]. Regarding the definition of a minimum in previous studies, it can be stated, that the definitions, including ours, varied a lot. In one study minima were classified as valleys with EA ≤ 50% regardless of further characteristics [21]. In another study there was no precise definition of minima described [9].

However, the number of minima reported in the previous studies per macro-reentrant ATs was consistent to our observations. In our population 2.4 minima per AT were detected, which is comparable to the ratio of 2 minima per ATs described in two others studies [9, 21]. One of the previous studies did further characterize the electrical activation minima with a median minimum EA level of 20% and median width of 31 ms, which is quite consistent to our results (median minimum level 22% and median width 24.5 ms) [21]. The described number of isthmi per minimum differed between 1.4 and 1.6 in the other studies and so was also comparable to our result of 1.8 isthmi per minimum [9, 22]. In our study, the sensitivity – suggested isthmi involves the CI – was very good with 98.2% with corresponds to the sensitivity of 100% in previous studies [9, 21]. In contrast, the specificity, stating that LP algorithm shows only the CIR, was with 12.3% quite low.

We analyzed different characteristics of our minima and tried to apply different preselection criteria in order to improve the specificity. Selecting the broadest minima (35.9±29.4 ms) resulted in a better specificity of 49.1% but came along with decreased sensitivity down to 80.7%. By the selection of the smallest minimum (average 14.4±9.8% EA), we were able achieve an equivalent improved specificity of 49.1% but still maintaining a quite good sensitivity of 91.2%. In addition, previous authors tried to further improve the quality of proposed isthmi by preselection of the corresponding minimum. They showed that a smaller minimum was associated with decreased isthmus dimensions, conduction velocity and increased EGM duration ($p<0.001$). Even more they showed that the level of minimum correlates closely with isthmus width, which is one of the most important CI characteristics [21]. Another study demonstrated that setting a low threshold for the minimum (they suggested minima ≤20% of max. EA) generates a better correlation with potential critical ablation sites. In macro-reentry tachycardia the specificity was 62.8% if the minimum was ≤20% but only 15.0% if the minimum was >20% [9]. These results are in line with our observations, taking the absolute minima of each AAF, characterized by ≤20% of max. EA (in 75.4% of cases),

we found a sensitivity of 95.3% and a specificity of 60.5%. Analyzing the broadest width (>50ms) of each AAF, showed an excellent sensitivity as well as specificity (100% and 90.0% respectively), but a width of least 50ms applied to only 17.5% of cases. Taken together selection of the smallest minima, represented by ≤20% of total EA, was commonly found and showed the best correlation with the CIR for a successful ablation leading to termination of the tachycardia.

Lumipoint® as a predictor of future AAF

During the follow-up of 10±7 months 42.3% of studied patients experienced a recurrence of a AAF, which is in line with previous data [23]. Taken the high recurrence rates despite the high initial ablation success it can be hypothesized that either initial ablation was not sufficient creating a complete isolation line or that initial bystander isthmus sites might become relevant in the future. To address this tissue, we evaluated if suggested isthmus sites during index procedure were predictive of potential CIR of future clinically relevant ATs. Our analysis revealed that all recurrent de-novo ATs (n=5), which were which were re-investigated and re-mapped in a second procedure, could be related potential CIR areas already suggested by the LP algorithm during the index procedure. Nevertheless, taken the fact that by far not every isthmus detected during the initial procedure study (n=248) was related to a clinically relevant AAF, the need for better understanding and preselection is given. Previous studies did not provide any data on this topic, therefore future studies should aim to evaluate the role of LP analysis with respect to the identification of arrhythmogenic substrates providing the pathophysiological basis for future arrhythmias.

Potential clinical implications

The occurrence of complex AT seems after ablation become more frequent due to multiple iatrogenic scars which lead to multiple conduction abnormalities which can be located within and outside the circuit as shown above [9]. Conservative strategies are often frustrating and so underline the importance of interventional treatment [5]. In scar areas, long-duration EGMs are usually highly fragmented and so catching up a meaningful time annotation can be challenging [24].

LP algorithm was developed to facilitate the three-dimensional course of a circulating wavefront in an easily interpretable two-dimensional format [21]. With a sensitivity of 98%, the preselection of potential ablation site can help to identify a critical ablation

site and thereby reduce mapping and procedure time. It could be helpful in less experienced operators to provide a guidance. Based on our data, the LP algorithms can be used for pre-selection, especially applying additional criteria like depth and width to detected AE minima. Nevertheless, this has still to be combined with the physician's interpretation of the reentry and the potentially most promising ablation area for persistent and fast success. In addition, our preliminary results suggest that LP might also be toll for substrate characterization, which might become relevant for future arrhythmias; however, this is matter of future research.

Limitations

This retrospective study is derived from a single-center experience and involves a limited number of patients and AAFs. Limitations apply for dual loop tachycardias, in which individual wavefronts can be maximal synchronized when they pass through a shared isthmus and so then overall EA is often minimal but does not necessary represent the perfect ablation site. Furthermore, wavefront collisions, isthmi outside the reentry tachycardia and undersampling can be reasons for misleading minima [21]. Further randomized studies are needed to evaluate the benefit in facilitate ablation procedures and improve outcomes. Especially if an ablation of additional isthmi during index procedure might lead to a reduction of recurrence of other AT forms in the future has to be evaluated in further studies.

Conclusion

The novel algorithm LP developed for the Rhythmia® mapping system provides new insights in characterization and illustration of CIRs of complex ATs. In our study, the tool showed an excellent sensitivity (98.2%), but poor overall specificity (12.3%) to detect CIR of the macro-reentry tachycardia. However, specificity could be significantly improved up to 60% accompanied by a still quite good sensitivity of 95% when selecting only the lowest EA minimum characterized by EA ≤20%. In addition, initial detected irrelevant bystander CIRs during the first AAF procedure might become relevant for future atrial flutter forms potentially identifying an arrhythmogenic substrate. Identification of target areas in the activation map bears the potential to provide a good preselection for potential critical isthmus regions improving procedural parameters and ablation success.

Tables

A. Baseline characteristics	**Overall (n=33)**
Age (years)	70.6 ± 13.2
Male, n (%)	18 (54.5)
Previous cardiac procedures, n (%)	28 (84.8)
Ablation, n (%)	23 (69.7)
PVI, n (%)	17 (51.5)
Post-cardiovascular surgery, n (%)	8 (24.2)
Post-interventional procedure, n (%)	3 (9.1)
LVEF, n (%)	50.2 ± 10.0
Medication (AAD), n (%)	30 (90.9)
Beta blocker, n (%)	30 (90.9)
Amiodaron, n (%)	8 (24.2)
Flecainid, n (%)	3 (9.1)
TIA/Stroke in history, n (%)	3 (9.1)
Coronary artery disease, n (%)	15 (45.5)
Arterial hypertension, n (%)	28 (84.8)
Diabetes mellitus, n (%)	6 (18.2)
Chronic kidney disease (GFR<60 ml/min/1,73m^2), n (%)	19 (57.6)
GFR>30 ml/min/1,73m^2, n (%)	18 (54.5)
GFR< 30 ml/min/1,73m^2, n (%)	1 (3.0)
Device, n (%)	15 (45.5)
Pacemaker, n (%)	11 (33.3)
1 chamber ICD, n (%)	2 (6.1)
CRT-D, n (%)	2 (6.1)

Table 1: Patients characteristics; n=33. Data are presents as n (%) or mean and standard deviation. Mean age was 70.6 years, more than half of patients were male and most of included patients took an antiarrhythmic drug. PVI: pulmonary vein isolation; LVEF: left ventricular ejection fraction; AAD: antiarrhythmic drugs; TIA: transitory ischemic attack; GFR: glomerular filtration rate; ICD: implantable cardiac defibrillator; CRT-D: cardiac resynchronization therapy defibrillator.

Electrophysiological characteristics	
Number of AAFs, n	57
AAFs in LA, n (%)	49 (86.0)
AAFs in RA, n (%)	8 (14.0)
Number of AAFs/patient, n	1.73
Cycle length of AAF, ms	291.0±70.2
Mapping time of atria, min	12.1±7.0
Conversion in sinus rhythm by ablation, n (%)	56 (98.2)
Number of minima, n	137
Number of minima/ AAF, n	2.4
Number of isthmi, n	248
Number of isthmi/ AAF, n	4.4
Number of isthmi/ minimum, n	1.8
Minima characteristics	
Level of EA minima, %	22.7±13.0
Width of minima, ms	24.5±22.1
EA peak pre-minimum, %	65.2±28.4
EA peak post-minimum, %	64.0±27.3

Table 2: Electrophysiological characteristics; Number of atrial tachycardia n=57. Data are presents as n (%) or mean and standard deviation. On average the cycle length was 291 ms and the mapping time of involved AAFs 12.1 minutes. Mean number of minima per AAFs was 2.4, mean number of isthmi 4.4. AAF: atrial tachycardia; LA: left atria; RA: right atria. AAF: atypical atrial flutter; EA: electrical activity.

Figures

Figure 1: (A) Left atria, view from the left. 'Skyline' tool displays on the right the histogram of global atrial surface activation during AAF cycle length, which shows the relative proportion of the atrial surface area that is activated at each point in time (electrical activity X axis), cycle length Y axis). The green line (length of 30 ms) marks the minimum (red box) of the skyline, which shows one isthmus (highlighted region, red arrow) in dorsal wall of LA. (B) Left atria, view from dorsal. One minimum involves two highlighted regions (red arrows) as potential CIR. (C) Example for three minima in the 'skyline'.

Figure 2: Distribution of minima and isthmi. (A) The skylines involve a total number of minima of 137. In most cases, 3 minima per AAF (39%) or 2 minima/AAF (26%). (B) The total number of highlighted areas corresponding to potential isthmi was 248. Analyses of the distribution show that in most cases 1 isthmus/minimum was shown (46%). (C) shows isthmi per AAF by decreasing order, most commonly the number is: ≥6 isthmi/AAF (26%).

Figure 3: (A) shows the proportion of detected isthmi, which are part of the AAF reentry circuit (61%). (B) illustrates sensitivity and specificity of the Lumipoint algorithm with respect to the detection the AAF-relevant CIR. Sensitivity represents detection of at least one relevant CIR by Lumipoint, which was 98.2%. Specificity was defined as detection of only reentry-relevant CIR, which was 12.3% in the unselected all-over analysis. (C) depicts sensitivity and specificity after applying the pre-selection criteria: analyzing the smallest electrical activation minimum only (left); selecting the broadest electrical activation minima (right). CIR: critical isthmus region; EA: electrical activity; AAF: atypical atrial flutter.

Figure 4: Characterization of minima predicting the potential CIR. (A) Detailed analysis regarding the role of depth of the minima; deepest minimum with higher specificity as well as sensitivity. (B) Detailed analysis regarding role of length; longer minima are associated with a higher sensitivity as well as specificity in contrast to shorter minima. (C) Detailed analysis regarding role of deepest minima of each AAF; deeper minima result in a better sensitivity and specificity in comparison to higher minima. (D) Detailed

analysis regarding role of width of minima; longer minima can better predict potentialIR than shorter minima. CIR: critical isthmus region; AAF: atypical atrial flutter.

Figure 5: Clinical outcome: Recurrence of AT in the follow up of 10±7 months (A). 20/33 patients have another AT: 30.3% patients another AAF, 18.2% a recurrence of AFib and 12.1% cases both. Of the patients with recurrent AAF (n=14), 50% (7/14) undergo re-ablation and two patients even twice. (B) illustrates the association of potential CIRs detected by LP algorithm during the index tachycardia in recurrent tachycardias during the index procedure. In total 13/33 patients showed a second flutter form; two patients develop even a third AAF form during the index procedure. In one case, the CIR is not detected by the LP algorithm. (C) Illustrates the association of potential CIRs detected by LP algorithm during the index procedure and involvement in recurrent tachycardias during follow-up. In all de-novo AAFs the potential CIR was already detected by LP during index procedure. AT: atrial tachycardia; FU: follow-up; AAF: atypical atrial flutter; AFib: atrial fibrillation; CIR: critical isthmus region; LP: Lumipoint®.

References

1. Chugh, A., et al., *Prevalence, mechanism, and clinical significance of macroreentrant atrial tachycardia during and following left trial ablation for atrial fibrillation*. Vol. 2. 2005. 464-71.
2. Patel, A.M., et al., *Atrial Tachycardia After Ablation of Persistent Atrial Fibrillation.* Circulation: Arrhythmia and Electrophysiology, 2008. **1**(1): p. 14-22.
3. Jais, P., et al., *A deductive mapping strategy for atrial tachycardia following atrial fibrillation ablation: importance of localized reentry.* J Cardiovasc Electrophysiol, 2009. **20**(5): p. 480-91.
4. Saghy, L., C. Tutuianu, and J. Szilagyi, *Atrial tachycardias following atrial fibrillation ablation.* Curr Cardiol Rev, 2015. **11**(2): p. 149-56.
5. Rostock, T., et al., *Characterization, mapping, and catheter ablation of recurrent atrial tachycardias after stepwise ablation of long-lasting persistent atrial fibrillation.* Circ Arrhythm Electrophysiol, 2010. **3**(2): p. 160-9.
6. Wakili, R., et al., *Recent advances in the molecular pathophysiology of atrial fibrillation.* J Clin Invest, 2011. **121**(8): p. 2955-68.
7. Shah, D., *Twelve-lead ECG interpretation in a patient with presumed left atrial flutter following AF ablation.* J Cardiovasc Electrophysiol, 2011. **22**(5): p. 613-7.
8. Martin, C.A., et al., *Use of Novel Electrogram "Lumipoint" Algorithm to Detect Critical Isthmus and Abnormal Potentials for Ablation in Ventricular Tachycardia.* JACC: Clinical Electrophysiology, 2019: p. 865.
9. Takigawa, M., et al., *Insights from atrial surface activation throughout atrial tachycardia cycle length: A new mapping tool.* Heart Rhythm, 2019.
10. Hocini, M., et al., *Techniques, evaluation, and consequences of linear block at the left atrial roof in paroxysmal atrial fibrillation: a prospective randomized study.* Circulation, 2005. **112**(24): p. 3688-96.
11. Jais, P., et al., *Technique and results of linear ablation at the mitral isthmus.* Circulation, 2004. **110**(19): p. 2996-3002.
12. Jais, P., et al., *How to perform linear lesions.* Heart Rhythm, 2007. **4**(6): p. 803-9.
13. Laţcu, D.G., et al., *Selection of Critical Isthmus in Scar-Related Atrial Tachycardia Using a New Automated Ultrahigh Resolution Mapping System.* Circ Arrhythm Electrophysiol, 2017. **10**(1).
14. Meyer, C., *High-density mapping-based ablation strategies of cardiac rhythm disorders: the RHYTHMIA™ experience at new horizons.* Europace, 2019. **21**(Supplement_3): p. iii7-iii10.
15. Schaeffer, B., et al., *Characterization, Mapping, and Ablation of Complex Atrial Tachycardia: Initial Experience With a Novel Method of Ultra High-Density 3D Mapping.* J Cardiovasc Electrophysiol, 2016. **27**(10): p. 1139-1150.
16. Takigawa, M., et al., *Revisiting anatomic macroreentrant tachycardia after atrial fibrillation ablation using ultrahigh-resolution mapping: Implications for ablation.* Heart Rhythm, 2018. **15**(3): p. 326-333.
17. Takigawa, M., et al., *Comprehensive Multicenter Study of the Common Isthmus in Post-Atrial Fibrillation Ablation Multiple-Loop Atrial Tachycardia.* Circ Arrhythm Electrophysiol, 2018. **11**(6): p. e006019.
18. Rostock, T., et al., *Chronic atrial fibrillation is a biatrial arrhythmia: data from catheter ablation of chronic atrial fibrillation aiming arrhythmia termination using a sequential ablation approach.* Circ Arrhythm Electrophysiol, 2008. **1**(5): p. 344-53.
19. Mesas, C.E., et al., *Left atrial tachycardia after circumferential pulmonary vein ablation for atrial fibrillation: electroanatomic characterization and treatment.* J Am Coll Cardiol, 2004. **44**(5): p. 1071-9.
20. Haissaguerre, M., et al., *Catheter ablation of long-lasting persistent atrial fibrillation: clinical outcome and mechanisms of subsequent arrhythmias.* J Cardiovasc Electrophysiol, 2005. **16**(11): p. 1138-47.
21. Moore, J.P., et al., *Ultrahigh-density mapping supplemented with global chamber activation identifies noncavotricuspid-dependent intra-atrial re-entry conduction isthmuses in adult*

congenital heart disease. Journal of Cardiovascular Electrophysiology, 2019. **30**(12): p. 2797-2805.
22. Alken, F.A., et al., *Advanced mapping strategies for ablation therapy in adults with congenital heart disease.* Cardiovasc Diagn Ther, 2019. **9**(Suppl 2): p. S247-s263.
23. Sultan, A., et al., *Predictors of Atrial Fibrillation Recurrence after Catheter Ablation: Data from the German Ablation Registry.* Sci Rep, 2017. **7**(1): p. 16678.
24. Bisceglia, C., A. Frontera, and P. Della Bella, *The LUMIPOINT™ software: are we just at the turning point?* EP Europace, 2019. **21**(Supplement_3): p. iii25-iii26.