



HAL
open science

Characterization of Complex Atrial Tachycardia in Patients With Previous Atrial Interventions Using High-Resolution Mapping

Nicolas Derval, Masateru Takigawa, Antonio Frontera, Saagar Mahida, Vlachos Konstantinos, Arnaud Denis, Josselin Duchateau, Xavier Pillois, Seigo Yamashita, Benjamin Berte, et al.

► **To cite this version:**

Nicolas Derval, Masateru Takigawa, Antonio Frontera, Saagar Mahida, Vlachos Konstantinos, et al.. Characterization of Complex Atrial Tachycardia in Patients With Previous Atrial Interventions Using High-Resolution Mapping. *JACC: Clinical Electrophysiology*, 2020, 6, pp.815 - 826. 10.1016/j.jacep.2020.03.004 . hal-03491594

HAL Id: hal-03491594

<https://hal.science/hal-03491594v1>

Submitted on 22 Aug 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Characterization of complex atrial tachycardia in patients with previous atrial interventions using high-resolution mapping

Nicolas Derval^{1,2}, MD, Masateru Takigawa^{1,2}, MD, PhD, Antonio Frontera^{1,2}, MD, PhD, Saagar Mahida³, MD, Vlachos Konstantinos^{1,2}, MD, Arnaud Denis^{1,2}, MD, Josselin Duchateau^{1,2,4}, MD, Xavier Pillois^{1,2}, PhD, Seigo Yamashita^{1,2}, MD, Benjamin Berte^{1,2}, MD, PhD, Nathaniel Thompson^{1,2}, MD, Darren Hooks¹, MD, Thomas Pambrun^{1,2}, MD, Frederic Sacher^{1,2,4}, MD, PhD, Méléze Hocini^{1,2,4}, MD, Pierre Bordachar, MD, PhD^{1,2,4}, Pierre Jaïs^{1,2,4}, MD, PhD and Michel Haïssaguerre^{1,2,4}, MD.

¹ IHU Liryc, Electrophysiology and Heart Modeling Institute, fondation Bordeaux Université, F-33600 Pessac- Bordeaux, France

² Bordeaux University Hospital (CHU), Cardio-Thoracic Unit, F-33600 Pessac, France

³ Department of Cardiac Electrophysiology and Inherited Cardiac Diseases, Liverpool Heart and Chest Hospital, United Kingdom

⁴ Univ. Bordeaux, Centre de recherche Cardio-Thoracique de Bordeaux, U1045, F-33000, Bordeaux, France

Running title: Complex atrial tachycardia and high-resolution mapping

Grants: This study received financial support from the French Government as part of the “Investments of the Future” program managed by the National Research Agency (ANR), Grant reference ANR-10-IAHU-04

Dr Derval N and Dr Takigawa contributed equally to this work

Conflict of interest:

Drs Derval, Denis, Sacher and Jaïs declare modest consulting fees and speaking honoraria from Boston Scientific.

The other authors report no conflicts

Corresponding author:

Dr Nicolas Derval.

CHU Bordeaux, Hôpital Cardiologique du Haut-Lévêque, 33604 Bordeaux-Pessac, France.

Tel: +33 5 57 65 64 71; Fax: +33 5 57 65 65 09

E-mail: nicolas.derval@chu-bordeaux.fr

Abstract (246 words)

Background

An incomplete understanding of the mechanism of atrial tachycardia (AT) is a major determinant of ablation failure.

Objectives

We systematically evaluated mechanisms of AT using the ultra high-resolution mapping in a large cohort of patients.

Methods

Consecutive patients with ≥ 1 AT (excluding cavotricuspid isthmus-dependent flutter) were included. Mapping was performed with 64-pole mapping catheter (ORIONTM, Rhythmia). The AT mechanism was defined based on activation mapping, and confirmed by entrainment in selected cases.

Results

132 patients were included (60 \pm 12 years; 31 [23%] female; 111 [84%] previous AF ablation; 5 [4%] previous left atriotomy). 104/111 (94%) of the post-AF ablation AT patients had substrate-based ablation during the index AF ablation. A total of 214 AT were mapped with complete definition of the AT mechanism in 206 (96%). 129 (60%) had anatomical macro-reentry (circuit diameter 44,2 \pm 9,6 mm), 57 (27%) had scar-related localized reentry (circuit diameter 25,8 \pm 12,2 mm), while only 20 (9%) had focal AT. 58 (45%) patients had multiple AT (27 [20%] dual-loop reentry; 60 [43%] sequential AT) with complex and highly variable transitions between AT circuits. 116/129 (90%) macro-reentrant AT, 56/57 (98%) localized AT, and 20/20 (100%) focal AT terminated following RF ablation. After 13 \pm 9 months' follow-up, 57 (46%) patients experienced AT recurrence.

Conclusion

Amongst patients with AT in the context of previous atrial interventions, particularly post-AF ablation patients, multiple complex AT circuits are common. Despite complete delineation of arrhythmia circuits using ultra-high resolution mapping and high acute ablation success rates, long-term freedom from AT is modest.

Condensed abstract: (127 words)

We systematically evaluated the mechanisms of AT in consecutive patients (excluding cavotricuspid isthmus-dependent flutter). 214 AT in 132 patients were mapped with definition of AT mechanism in 206. 129 had macro-reentry, 57 had localized reentry, and 20 had focal AT. 66 patients had multiple AT with complex transitions between AT circuits. 116/129 macro-reentrant AT, 56/57 localized AT, and 20/20 focal AT terminated following radiofrequency ablation. After 13 \pm 9 months follow-up, 57 (46%) patients experienced AT recurrence. Our findings indicate that amongst patients with complex AT multiple AT circuits are common. Despite complete delineation of arrhythmia circuits and termination rate, long-term freedom from AT is modest.

Keywords:

Atrial tachycardia, catheter ablation, atrial fibrillation, cardiac mapping

List of abbreviations:

AT: atrial tachycardia

AF: atrial fibrillation

CT Imaging: Computerized Tomography imaging

ACT: Activated Clotting Time

EGM: Electrogram

TCL: Tachycardia Cycle Length

PPI: Post Pacing Interval

ECG: Electrocardiogram

PVI: Pulmonary Vein Isolation

RF: Radiofrequency
CTI: Cavo-tricuspid Isthmus
RA: Right Atria
CFAE: Complex Fragmented Atrial Electrogram

Introduction

Ablation of complex atrial tachycardias (AT) is commonly associated with prolonged procedure times and in certain circumstances, modest success rates. AT in patients with prior substrate-based AF ablation may be associated with particularly complex substrates. An incomplete understanding of the arrhythmia mechanism is an important determinant of ablation failure. The development of ultra high-resolution mapping techniques designed for automated generation of highly detailed activation maps has the potential to enhance procedural outcomes and potentially provide novel insights into arrhythmia mechanisms. Early results from studies using ultra high-resolution mapping (Rhythmia, Boston scientific) have reported that the technology accurately identifies complex AT mechanisms (1–3). However, these studies have largely been restricted to small cohorts of patients. In the present study we systematically evaluated AT mechanisms using the Rhythmia in a large consecutive cohort of patients (excluding cavotricuspid isthmus-dependent flutter).

Methods

Patient population

Consecutive patients referred for ablation of AT between November 2014 and October 2016 were included. Patients with a clinical presentation of a cavotricuspid isthmus-dependent flutter were not included in the study. The presence of left atrial dilatation or structural heart disease did not represent an exclusion criterion. The study was approved by the Institutional Review Board at Hôpital Haut Lévêque.

Mapping and ablation

Procedures were performed under conscious sedation using the Rhythmia mapping system. Patients were established on oral anticoagulation for at least one-month pre-ablation.

Transoesophageal echocardiography or CT imaging was performed within 48 hours of the procedure to exclude the presence of thrombus. Unfractionated heparin was administered before the transseptal access with a target activated clotting time (ACT) of 300 – 400 sec. A deflectable decapolar catheter (Dynamic XT Boston Scientific) was positioned within the coronary sinus. If the patient was in sinus rhythm at the start of the procedure, burst pacing was performed to induce AT. The patient was excluded from analysis if: 1) the AT was not inducible; 2) atrial fibrillation or unstable AT was induced; 3) if the AT was mechanically terminated before the AT was completely mapped (Figure 1).

A steerable long sheath (Agilis, St Jude Medical) and Intella Map Orion™ Catheter (Boston Scientific, MA) was used for mapping. A dedicated automated algorithm (Rhythmia® software) was used for activation mapping. A combination of peak EGM amplitude, relative timing to surrounding EGMs, and EGM proximity to the atrial 3D model was used for automated generation of activation maps. Automated point acquisition was performed using the following beat acceptance criteria: 1) tachycardia cycle length (TCL) stability (± 10 ms); 2) time stability of a reference EGM from the coronary sinus catheter (± 5 ms); 3) beat-to-beat EGM consistency; 4) EGMs acquired during the expiration phase; 5) EGMs acquired during stable position of the catheter (< 1 mm catheter movement during acquisition window); 6) tracking quality of the mapping catheter to ensure correct location of the mapping catheter. Activation timing of local fragmented EGMs was largely determined by the automatic annotation software. Manual re-annotation was performed in a small subset of cases. Complementary entrainment mapping was performed for validation of complex circuits, especially in the presence of double reentry. The following thresholds were used for definition of scar; scar < 0.05 mV; scar borderzone 0.05 and 0.5 mV; normal 0.5 mV. A 3.5mm

irrigated-tip catheter (SF catheter, Biosense Webster, Diamond Bar, CA) was used for ablation.

Classification of atrial tachycardia

The AT mechanism was classified as follows:

1. Macro re-entry was defined by activation recorded over the entire AT CL circling around an anatomical obstacle and entrainment with post-pacing interval (PPI) = CL at ≥ 2 opposite segments consistent with a re-entrant mechanism
2. Localized scar related re-entry was defined by atrial activation that was recorded over the entire ATCL circling around a localized area. The localized re-entry circuit was variable in size and was composed of a scar with conduction block and a channel of slow conduction consistent with an "isthmus".
3. Focal atrial tachycardia was defined as atrial activity originating from a discrete site activating the surrounding tissue centrifugally (not necessarily recorded over the entire ATCL).
4. Dual-loop AT was defined as re-entrant AT composed of two independent active circuits sharing one common path. The entire cycle length has to be included in each of the circuits. The active participation of each circuit is confirmed by entrainment (4). In case of dual-loop AT only the circuit targeted by ablation was accounted for in each AT category.

Isthmus measurements

The length of the entire circuit was measured on the geometry created by the Rhythmia system. The shortest length of the isthmus was measured on the geometry. The electrogram voltage, amplitude and duration on the narrowest site in the common isthmus were measured if 3 consecutive stable EGM were recorded.

Follow-up and study endpoints

The end point of the procedure was termination of AT(s) by ablation to sinus rhythm, demonstration of bi-directional block across ablation lines and non-inducibility of any atrial tachyarrhythmia. Inducibility was tested exclusively by burst pacing from two different pacing sites (left atrial appendage and coronary sinus), down to 220 ms (or the local refractory period, if >220 ms) and repeated three times. If the clinical AT converted to a different AT or in the event of induction of another AT, the ablation was continued aiming at termination to sinus rhythm.

All patients were seen at 3, 6 and 12 months' post-ablation in the outpatient clinic. At each visit, the patients were investigated with a 24-hour Holter monitor, exercise stress test and echocardiography. Follow-up visits at 1 and 9 months were organized by the referring physicians (with 24-hour Holter monitoring). In case of symptoms, an additional 12-lead ECG was acquired. Antiarrhythmic drug treatment, including amiodarone, was discontinued after the procedure in all patients. Patients with more than one recurrence of AT were scheduled for re-do procedures and antiarrhythmic drug treatment was re-initiated, (unless contraindicated), as a bridge to the re-do ablation procedure.

Statistical analysis

Continuous data are expressed as mean±SD. Comparison between groups was carried out using a Student t-test or a one way ANOVA and Bonferroni post-hoc test. Categorical variables were expressed as absolute numbers (percentages) and compared using Pearson Chi square test or the Fisher exact test when appropriate. Values of $P < 0.05$ were considered significant.

Results:

Patient characteristics

160 patients were enrolled in the study. Twenty-eight patients were subsequently excluded due to either intra-procedural induction of AF, induction of unstable AT (that degenerated into AF), or incomplete mapping of the arrhythmia. The baseline characteristics of the 132 included patients are summarized in Table 1. 111/132 (80%) had post-AF ablation AT, 5 (4%) had post-surgical AT, 16 (12%) had ATs in native atria. Amongst the 111 patients with post-AF ablation AT, the index AF ablation procedure involved substrate-based ablation (with AF termination as the procedural endpoint) in 104 (94%) cases. The index AF ablation procedure involved a sequential approach (PVI, conventional EGM-based ablation, and linear lesions) in 77 (70%), a substrate-based approach guided by non-invasive body surface mapping in 27 (24%), and PVI only in 7 (6%, all patients with RF ablation, Table 2). 42 patients had a single AF ablation procedure while 69 had ≥ 2 AF ablation procedures. The strategies for the sequential approach and ECGI-based ablation have been described in detail previously (5)(6).

Mapping

214 sustained AT were mapped in the above 132 patients (1 AT in 74 [56%]; 2 AT in 38 [29%]; 3 AT in 16 [12%] and 4 AT in 4 [3%]). Left atrial mapping was performed in all cases (15200 \pm 7683 points/map; 924 \pm 484 sec/map). Right atrial mapping was performed in 45 (21%) cases (8238 \pm 7596 points/map; 601 \pm 534 sec/map). Mapping characteristics are included in Table 3. Manual re-annotation was performed in 22 (10%) cases. When re-annotation was performed, the number of re-annotated points was limited to ≤ 6 points/map. The reason for re-annotation was always related to the noise/signal ratio in localized areas of the atria with

very low-voltage signals. These re-annotated points were never critical to understanding the circuit itself but re-annotation improved the overall activation map. The mechanism of atrial tachycardia was completely defined for 206/214 (96%) ATs (129 [60%] macro-reentry; 57 [27%] localized reentry; 20 [9%] focal AT). Entrainment was performed in the majority of cases (200 of the 214 AT, 93%) with a mean of 3 ± 2 entrainment sites per AT. The AT subtypes are described in more detail in subsequent sections (Figure 2). Despite detailed mapping, the mechanism of the remaining 8 (4%) ATs remained incompletely defined.

AT subtypes

Macro-reentrant AT

The 129 macro re-entrant AT were identified in 93 patients (83 [86%] post-AF ablation patients; 6 [6%] native atria and 4 [4%] previous cardiac surgery). 100% of the AT CL was mapped in the atria in all patients (AT CL 277 ± 62 ms). 72/129 (56%) were peri-mitral, 38 (29%) were roof-dependent, 16 (12%) were CTI-dependent, 2 (1%) were bi-atrial, 1 (1%) were right atrial (summarized in Figure 1, 3 and 4). All the 16 CTI-dependent AT were part of multiple sequential AT (15 in post-AF ablation patients and 1 in native atria). Overall, the length of the targeted isthmus was 15 ± 9 mm. EGMs recorded at the critical isthmus had the following characteristics: fragmented in 94 (73%) ATs; amplitude: 0.43 ± 0.68 mV; longest duration: 83.2 ± 36.3 ms and covering less than a third of the AT CL (mean $29\pm 12\%$). The total size of the AT circuit (diameter) was 44.2 ± 9.6 mm (range: 20 to 71 mm). 115/129 (89%) target ablation sites (for linear ablation) were selected anatomically (58 mitral lines; 38 roof lines; 16 CTI lines; 2 bi-atrial lines and 1 upper RA line). In 14/129 (11%) cases (all peri-mitral) a more practical alternative ablation line was identified based on mapping characteristics (antero-septal in 12 cases and postero-septal in 2 cases). 116/129 ATs (90%) terminated following ablation (RF time 430 ± 688 sec). Among the 10 ATs that did not

terminate with ablation, 9 were peri-mitral and 1 was bi-atrial. Isthmus characteristics are included in Table 4. In all 10 cases, the ablation failure was due to failure to achieve mitral line block. The relationship between the index AF ablation strategy and the macro re-entrant AT mechanism is included in Table 2 and Figure 4.

Localized reentry

The 57 localized re-entry AT were identified in 47 patients (37 [79%] post-AF ablation patients; 8 [17%] native atria; and 2 [4%] previous cardiac surgery). 100% of the AT CL was mapped in all patients (AT CL 287 ± 76 ms). Localized scar (with or without functional block) was identified in 100% cases. 18/37 (49%) AT in the post-ablation group involved ≥ 1 gap in the pulmonary vein circumferential ablation line. Figure 3 summarizes the anatomic distribution of localized re-entry circuits. The critical AT isthmus was defined as the narrowest path of the tachycardia circuit (mean 11.8 ± 7.2 mm). EGMs at the critical isthmus sites were highly fragmented in all AT (amplitude 0.20 ± 0.22 mV; longest duration $113,6\pm 51,7$ ms). The EGMs at the critical isthmus covered $>30\%$ of the AL CL in 36/57 (63%) AT, mean $40\pm 17\%$. The total size of the AT circuit was $25,8\pm 12,2$ mm (range: 8 to 56 mm). RF ablation at the isthmus site terminated 56/57 98% of the AT (RF time 161 ± 223 sec). The only RF ablation failure occurred in a patient with a septal circuit. The relationship between the index AF ablation strategy and localized re-entry AT is included in Table 2.

Focal AT

The 20 focal ATs were identified in 17 patients (10 post-AF ablation; 7 native atria). Focal AT was diagnosed based on the identification of a discrete point source of the AT. The clustering of focal AT is illustrated in Figure 3. More than 90% of the AT CL was identified in the LA for only 3/20 (15%) ATs. The mean AT CL was 305 ± 84 ms. 11/20 (55%) EGMs at

the earliest site of activation were fragmented (amplitude 0.65 ± 0.60 mV; duration: $65,6\pm 45,4$ ms). RF ablation at the earliest activation site terminated 100% of the AT (RF time 106 ± 189 sec). The relationship between the index AF ablation strategy and focal AT is included in Table 2.

Multiple atrial tachycardias

In the overall cohort, 58 (45%) patients had multiple mapped AT. Furthermore, in 6 patients, despite the fact that sinus rhythm was restored after ablation of a single isthmus, a dual loop re-entry circuit with two isthmuses was mapped during AT (all perimitral + roof AT). In all 6 patients, the second isthmus was subsequently targeted without re-mapping. Therefore, a total of 64 (50%) patients were considered to have multiple AT for the purpose of our analysis.

Multiple ATs fell into one of two categories; (1) dual-loop reentry (27 [20%]) and (2) sequential AT (60 [43%]). The 27 dual-loop AT were identified in 24 patients (22 post-AF ablation; 3 native atria). 22/27 (81%) dual-loop AT were peri-mitral + roof dependent, 4 (15%) involved peri-mitral + localized re-entry and 1 (4%) was roof dependent + localized re-entry. 58 patients had sequentially mapped AT (2 AT n=38; 3 AT n=16; 4 AT n=4). The mean AT CL progressively prolonged from the initial circuit to successive circuits (Figure 5, 6). In the subset of patients with post-AF ablation AT, 37/77 (48%) with a sequential approach during the index AF ablation had multiple AT (2 AT n=27; 3 AT n=8; 4 AT n=2; total of 126 AT). 9/27 (33%) patients with previous ECGI-based ablation had multiple AT (2 AT n=3; 3 AT n=4; 4 AT n=2; total of 44 AT). 1/9 (11%) patients with PVI-only as the index procedure had multiple AT. As summarized in Figure 7A-C, amongst patients who had sequential or ECGI-based ablation, multiple complex transitions between different AT mechanisms were observed with highly variable transitions between patients.

Relationship between underlying substrate and AT subtypes

The relationship between the underlying substrate and the AT mechanism is summarized in Figure 4 and Table 2.

Follow-up

124 patients completed a follow-up period of 13 ± 9 months, 57 (46%) patients experienced recurrences of AT. 67 patients remained free of any arrhythmia recurrence. Amongst the 111 post-AF ablation patients with complete follow-up, 51 (46%) patients experienced recurrences. The specific recurrence rate for each AT subtype was: 35/71 (49%) in patients with macro-reentrant AT, 10/30 (33%) in patients with localized re-entry and 2/5 (40%) in patients with focal AT.

Re-do procedures

27/57 (47%) patients had a re-do ablation procedure. In 19 (70%) of the patients undergoing a re-do procedure, the recurrent AT mechanism was anatomical macroreentry related either to (1) recovery of conduction through the mitral isthmus (15 [79%] patients) or (2) recovery of conduction through the roof line (4 [21%] patients). In 8 (30%) patients, the recurrent AT mechanism was localized re-entry.

Discussion

In a large consecutive series of patients undergoing ultra high-resolution mapping for AT, we demonstrate that: 1) amongst patients with post-AF ablation AT, multiple complex AT are common, with between a third and a half of patients displaying multiple AT, with complex transitions between different AT mechanisms, 2) despite complete delineation of arrhythmia circuits using ultra-high resolution mapping and high acute ablation success rates, AT

recurrences are common amongst these patients, 3) re-entry is the predominant AT mechanism in patients with previous AF ablation, with focal AT accounting for only a small minority of cases, 4) amongst the patients with macro re-entry, more than a fifth have complex dual-loop circuits, 5) amongst the patients with localized re-entry, the majority of circuits are not micro re-entrant, but rather demonstrate larger, more heterogeneous circuits.

In the present study, we demonstrate the highly complex nature of AT in patients with different underlying substrates. Amongst patients who have previously undergone substrate-based AF ablation, re-entry remains the predominant substrate for complex left AT. Of note, the initial ablation strategy in this group of patient were similar by the final endpoint (sinus rhythm restoration) but using different strategy. Linear lesion were almost systematic in the EGM guided group while it was limited in the ECGI guided. However, the type of recurrent AT distribution appears irrespective of the initial ablation strategy. While the acute success rates following ablation were favorable, the procedures involved extensive mapping of multiple complex AT with complex transitions between AT circuits. Furthermore, despite a detailed understanding of arrhythmia circuits and acute success, patients had high recurrence rates during follow-up.

Using ultra-high resolution mapping, we identified a very low prevalence of focal AT, particularly amongst post-AF ablation patients. The relative prevalence of focal AT is lower than previous reports on post-AF ablation AT (7, 8). Consistent with previous reports however, the focal ATs demonstrated a preponderance towards venous structures.(9–11)(12). Interestingly, close to half of the ATs were localized at the upper part of the left atrial ridge, which is in close proximity to the distal part of the Marshall bundle. The Marshall bundle represents a complex epicardial structure that has the potential to support re-entry. It could be

speculated therefore that the ‘focal’ ATs identified in this region could in fact be the focal breakthrough of a partially epicardial re-entry circuit (13). By implication therefore, an even lower proportion of the ATs may be focal.

Close to two-thirds of AT in our cohort were due to macro re-entry, with the majority being either peri-mitral or roof-dependent. In a recent small case-series, we reported that complex and atypical circuits are not uncommon in patients with macro-re-entrant AT. The present study expands on these findings with the identification of a relatively high prevalence of complex dual-loop circuits. Furthermore, we demonstrate that a combination of ultra high-density mapping and entrainment accurately identifies the complex AT circuit in a high proportion of cases (2). Previous studies have demonstrated that treatment of macro-re-entrant AT and more specifically, durable block of the mitral isthmus line was difficult to achieve. The implication of the Marshall bundle acting as an insulated by-pass tract, may account for our high recurrence rate despite a high rate of acute block (53/62 [86%]) (14)(15)(16)(17)(18).

Close to a third of AT in our cohort were due to localized re-entry circuits. These ATs occurred almost exclusively in regions of atrial scar with the critical isthmus located within very low voltage areas: Critical isthmus sites consistently displayed low amplitude, fractionated signals of long duration. The localized circuits identified by ultra high-resolution mapping were relatively large with a mean length of 3 cm. Our findings suggest that contrary to previous reports, micro re-entrant circuits are relatively uncommon and a large proportion of ATs are due to larger circuits with significant heterogeneity in terms of size. We believe that ultra high-resolution mapping is more likely to accurately delineate the re-entry circuit. Our findings suggest that localized re-entry circuits are defined by tissue characteristics of the circuit (scar-related borders) and the size of the circuit appears less relevant. Therefore, we

used a classification of AT that was based on the nature of the circuit (anatomic obstacle or scar) and not on the size of the circuit per se to avoid overlap between the different types of re-entry (19).

Clinical implications for persistent AF ablation

Prior substrate-based ablation for AF was the predominant substrate for complex left AT in this consecutive case-series. Based on our previously reported data, more than half of patients who undergo stepwise AF ablation experience AT recurrence (after one or two procedures). Amongst patients undergoing ECGI ablation, the AT recurrence rates are estimated at 40% (unpublished data). Similar results have been reported in studies using different substrate modification protocols.(20)(21). While, macroreentry was the predominant AT mechanism in our cohort (two-thirds of cases), the re-entrant circuits were highly complex, and necessitated prolonged procedures for AT termination. Furthermore, it is important to emphasize that despite a high acute success rate of AT termination and blocked lines, almost half of our patients experienced AT recurrence. There are a number of potential factors that may contribute to post-AF ablation AT susceptibility, including incomplete elimination of electrograms at target sites (particularly rotor and CFAE sites), development of scar and scar borderzone despite adequate ablation, and failure to block anatomical lines. Of note, our follow-up results, which have been confirmed by a separate study from our group, demonstrate that the main reasons for AT recurrence after high-density map guided ablation are: (1) perimitral flutter involving epicardial connections (vein of Marshall) for patients in whom the index AT was anatomical macro-reentry; (2) a different localized re-entry circuit for patients in whom scar-related AT was the index AT (Takigawa et al, in press). Overall, our findings underscore the need for novel, more effective substrate-based ablation techniques for AF that have lower longer term pro-arrhythmogenic potential.

Limitations

Our study population consisted of consecutive AT cases, with a high proportion being post-AF ablation AT. Therefore, AT in post-surgical patients and patients with native atria are underrepresented. Treatment of AT specifically targeting the critical isthmus might be an interesting strategy however most of our cases were a combination of scar related localized AT and macroentry. In addition to ablation of critical AT isthmus sites, ablation of other sites (including pulmonary vein re-isolation and completion of lines from previous procedures) is a confounding factor for analysis of the impact of isthmus ablation. The specific strategy for substrate-based ablation in patients with previous AF ablation is an important determinant of the AT mechanisms. However, due to a lack of data on the exact location of previous ablation sites, we were unable to make a correlation between previous substrate ablation and AT mechanisms in our cohort. It is likely that most current ablation strategies besides PV isolation produce substrate for subsequent AT without a clear relationship between the chosen strategy and the AT mechanisms. However, the distribution of AT mechanisms observed in our study are related to the initial ablation strategy and may not be similar with a different substrate ablation. We have not performed direct epicardial mapping in patients with a suspected epicardial connection therefore our understanding of these potential connections remains speculative. Finally, a significant proportion of the AF ablation cases were performed prior to the widespread use of cryoballoon ablation and contact force-guided RF ablation. Therefore, the results may not be directly transferrable to patients who undergo ablation using these technologies.

Clinical perspectives

The present study highlights the complexity of managing atypical AT especially in post-atrial fibrillation ablation patients. Despite accurate characterization of the AT mechanism and a high acute termination rate following ablation, the recurrence rate remains high. In half of the

patients, multiple complex AT circuits with variable transition between circuits were observed, resulting in prolonged and challenging procedures. Our results suggest that (1) AT ablation strategies should be more comprehensive, and in addition to targeting the clinical AT, should also evaluate how potential AT circuits could contribute to future arrhythmia recurrence; (2) given the high rate of complex AT recurrences, there is a need for re-evaluation of current substrate-ablation strategies for AF.

Figures legends

Figure 1 – CENTRAL ILLUSTRATION: Flowchart of the study with a summary of the principal characteristics of each type of atrial tachycardia.

Figure 2: Example activation map of the three atrial tachycardia subtypes: A: focal atrial tachycardia, B: scar related localized reentrant AT, C: Anatomical macro-reentrant AT

Figure 3: Anatomical distribution of the different types of atrial tachycardia. Left panel: *blue star*: focal tachycardia in patients with native atria; *red star*: focal tachycardia in patients with post AF ablation substrate.

Figure 4: Distribution of the different type of macro-reentrant AT in each arrhythmia substrate (BiAT: Biatrial tachycardia, CTI: cavotricuspid isthmus dependant flutter, PM: perimtral AT).

Figure 5: Evolution of atrial tachycardia cycle length in patients with multiple AT. (*: $p=0.01$)

Figure 6: Sequential mapping of three consecutives atrial tachycardia in a single patient with post-AF ablation substrate. Note that the different AT are always centered by scar or an anatomical obstacle and that the boundaries of the circuit are also drawn by scar.

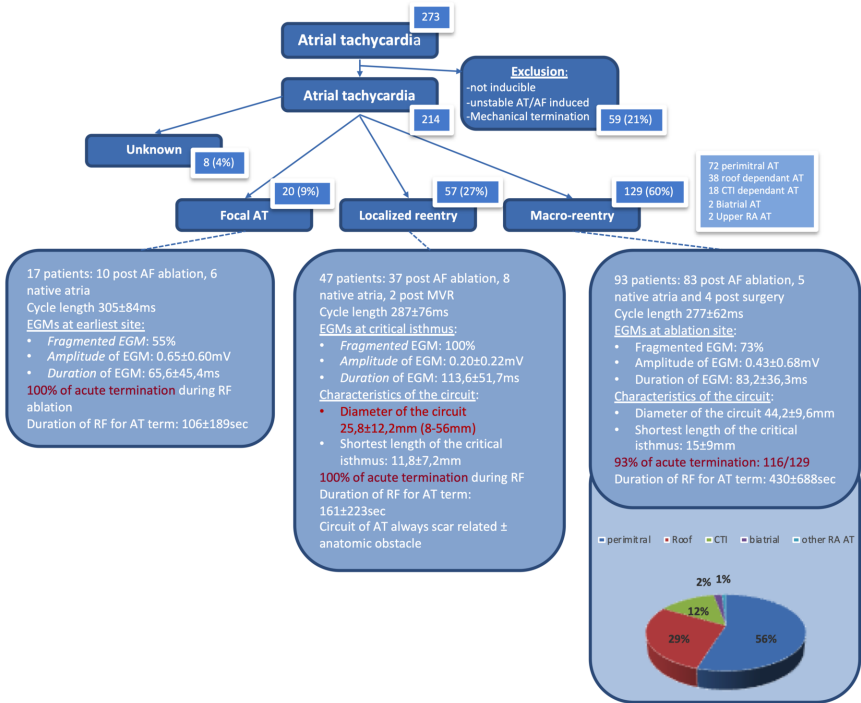
Figure 7: Characteristics of atrial tachycardia in patients with post AF ablation substrate depending on the initial ablation strategy. A: EGM guided strategy (stepwise); B: ECGi guided strategy; C: PVI only strategy. *Upper panel*: main characteristics and repartition of the number of atrial lines that had to be done at the end of that ablation process. *Lower panel*: distribution of AT types in patients with multiple AT.

References

1. Anter E, Tschabrunn CM, Contreras-Valdes FM, Li J, Josephson ME. Pulmonary vein isolation using the Rhythmia mapping system: Verification of intracardiac signals using the Orion mini-basket catheter. *Hear. Rhythm* 2015;12:1927–1934. Available at: <http://dx.doi.org/10.1016/j.hrthm.2015.05.019>.
2. Takigawa M, Derval N, Frontera A, et al. Revisiting anatomic macroreentrant tachycardia after atrial fibrillation ablation using ultrahigh-resolution mapping: Implications for ablation. *Hear. Rhythm* 2018;15:326–333. Available at: <https://doi.org/10.1016/j.hrthm.2017.10.029>.
3. Lațcu DG, Bun S-S, Viera F, et al. Selection of Critical Isthmus in Scar-Related Atrial Tachycardia Using a New Automated Ultrahigh Resolution Mapping System. *Circ. Arrhythmia Electrophysiol.* 2017;10:e004510. Available at: <http://circep.ahajournals.org/lookup/doi/10.1161/CIRCEP.116.004510>.
4. Takigawa M, Derval N, Maury P, et al. Comprehensive Multicenter Study of the Common Isthmus in Post–Atrial Fibrillation Ablation Multiple-Loop Atrial Tachycardia. *Circ. Arrhythmia Electrophysiol.* 2018;11:e006019. Available at: <http://circep.ahajournals.org/lookup/doi/10.1161/CIRCEP.117.006019>.
5. O’Neill MD, Jaïs P, Takahashi Y, et al. The stepwise ablation approach for chronic atrial fibrillation - Evidence for a cumulative effect. *J. Interv. Card. Electrophysiol.* 2006;16:153–167.
6. Haissaguerre M, Hocini M, Denis A, et al. Driver Domains in Persistent Atrial Fibrillation. *Circulation* 2014;130:530–538. Available at: <https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.113.005421>.
7. Rostock T, Drewitz I, Steven D, et al. Characterization, mapping, and catheter ablation of recurrent atrial tachycardias after stepwise ablation of long-lasting persistent atrial fibrillation. *Circ. Arrhythmia Electrophysiol.* 2010;3:160–169.

8. Gerstenfeld EP, Callans DJ, Dixit S, et al. Mechanisms of organized left atrial tachycardias occurring after pulmonary vein isolation. *Circulation* 2004;110:1351–1357.
9. Mohamed U, Skanes AC, Gula LJ, et al. A novel pacing maneuver to localize focal atrial tachycardia. *J. Cardiovasc. Electrophysiol.* 2007;18:1–6. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17081203>. Accessed May 23, 2012.
10. Badhwar N, Kalman JM, Sparks PB, et al. Atrial tachycardia arising from the coronary sinus musculature: Electrophysiological characteristics and long-term outcomes of radiofrequency ablation. *J. Am. Coll. Cardiol.* 2005;46:1921–1930.
11. Medi C, Kalman JM, Haqqani H, et al. Tachycardia-Mediated Cardiomyopathy Secondary to Focal Atrial Tachycardia. Long-Term Outcome After Catheter Ablation. *J. Am. Coll. Cardiol.* 2009;53:1791–1797. Available at: <http://dx.doi.org/10.1016/j.jacc.2009.02.014>.
12. Haïssaguerre M, Sanders P, Hocini M, et al. Catheter ablation of long-lasting persistent atrial fibrillation: critical structures for termination. *J. Cardiovasc. Electrophysiol.* 2005;16:1125–37. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16302892>. Accessed November 5, 2012.
13. Vlachos K, Denis A, Takigawa M, et al. The role of Marshall bundle epicardial connections in atrial tachycardias after atrial fibrillation ablation. *Hear. Rhythm* 2019. Available at: <https://doi.org/10.1016/j.hrthm.2019.05.019>.
14. Briceño DF, Valderrábano M. Recurrent perimitral flutter due to vein of marshall epicardial connections bypassing the mitral isthmus response to ethanol infusion. *Circ. Arrhythmia Electrophysiol.* 2014;7:988–989.
15. Hojo R, Fukamizu S, Kitamura T, Maeno K, Hiraoka M, Sakurada H. Pseudo-conduction block at the mitral isthmus in a patient with epicardial impulse propagation through the vein of Marshall. *Hear. Case Reports* 2015;1:232–237. Available at: <http://linkinghub.elsevier.com/retrieve/pii/S221402711500072X>.

16. Chugh A, Gurm HS, Krishnasamy K, et al. Spectrum of atrial arrhythmias using the ligament of Marshall in patients with atrial fibrillation. *Hear. Rhythm* 2017. Available at: <http://linkinghub.elsevier.com/retrieve/pii/S1547527117309578>.
17. Báez-Escudero JL, Morales PF, Dave AS, et al. Ethanol infusion in the vein of Marshall facilitates mitral isthmus ablation. *Hear. Rhythm* 2012;9:1207–1215. Available at: <http://dx.doi.org/10.1016/j.hrthm.2012.03.008>.
18. Kitamura T, Vlachos K, Denis A, et al. Ethanol infusion for Marshall bundle epicardial connections in Marshall bundle related atrial tachycardias following atrial fibrillation ablation: the accessibility and success rate of ethanol infusion by using a femoral approach. *J. Cardiovasc. Electrophysiol.* 2019;jce.14019. Available at: <https://onlinelibrary.wiley.com/doi/abs/10.1111/jce.14019>.
19. Calkins H, Hindricks G, Cappato R, et al. TEMPORARY REMOVAL: 2017 HRS/EHRA/ECAS/APHRS/SOLAECE Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation. *Hear. Rhythm* 2017;14:e275–e444. Available at: <http://linkinghub.elsevier.com/retrieve/pii/S1547527117305908>.
20. Ammar S, Hessling G, Reents T, et al. Arrhythmia type after persistent atrial fibrillation ablation predicts success of the repeat procedure. *Circ. Arrhythmia Electrophysiol.* 2011;4:609–614.
21. Wynn GJ, Das M, Bonnett LJ, Panikker S, Wong T, Gupta D. Efficacy of Catheter Ablation for Persistent Atrial Fibrillation: A Systematic Review and Meta-Analysis of Evidence from Randomised and Non-Randomised Controlled Trials. *Circ. Arrhythmia Electrophysiol.* 2014:CIRCEP.114.001759-. Available at: <http://circep.ahajournals.org/content/early/2014/08/16/CIRCEP.114.001759.abstract?papetoc>.



273

Atrial tachycardia

Atrial tachycardia

Exclusion:
 --not inducible
 --unstable AT/AF induced
 --Mechanical termination

59 (21%)

Unknown

8 (4%)

Focal AT

20 (9%)

Localized reentry

57 (27%)

Macro-reentry

129 (60%)

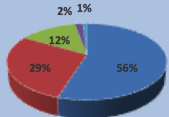
72 perimitral AT
 38 roof dependant AT
 18 CTI dependant AT
 2 Batrial AT
 2 Upper RA AT

17 patients: 10 post AF ablation, 6 native atria
 Cycle length 305±84ms
EGMs at earliest site:
 • *Fragmented EGM:* 55%
 • *Amplitude of EGM:* 0.65±0.60mV
 • *Duration of EGM:* 65,6±45,4ms
100% of acute termination during RF ablation
 Duration of RF for AT term: 106±189sec

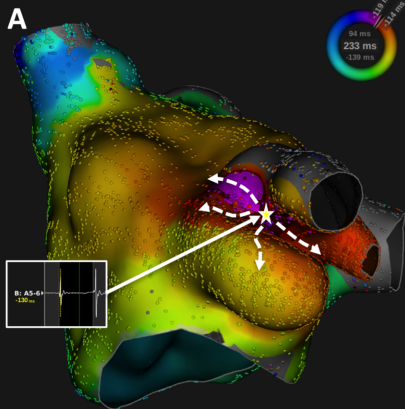
47 patients: 37 post AF ablation, 8 native atria, 2 post MVR
 Cycle length 287±76ms
EGMs at critical isthmus:
 • *Fragmented EGM:* 100%
 • *Amplitude of EGM:* 0.20±0.22mV
 • *Duration of EGM:* 113,6±51,7ms
Characteristics of the circuit:
 • **Diameter of the circuit** 25,8±12,2mm (8-56mm)
 • Shortest length of the critical isthmus: 11,8±7,2mm
100% of acute termination during RF
 Duration of RF for AT term: 161±223sec
 Circuit of AT always scar related ± anatomic obstacle

93 patients: 83 post AF ablation, 5 native atria and 4 post surgery
 Cycle length 277±62ms
EGMs at ablation site:
 • *Fragmented EGM:* 73%
 • *Amplitude of EGM:* 0.43±0.68mV
 • *Duration of EGM:* 83,2±36,3ms
Characteristics of the circuit:
 • Diameter of the circuit 44,2±9,6mm
 • Shortest length of the critical isthmus: 15±9mm
93% of acute termination: 116/129
 Duration of RF for AT term: 430±688sec

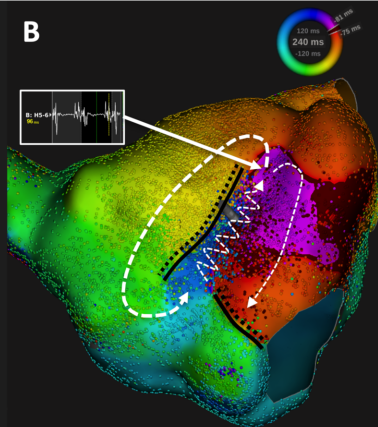
perimitral 2% | Roof 1% | CTI 12% | Batrial 29% | other RA AT 56%



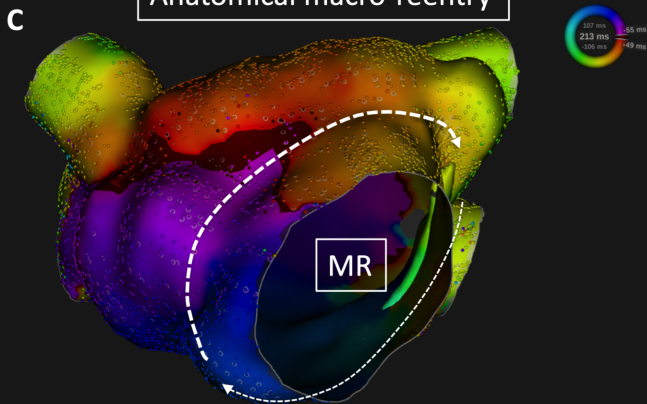
Focal AT



Scar-related localized reentry

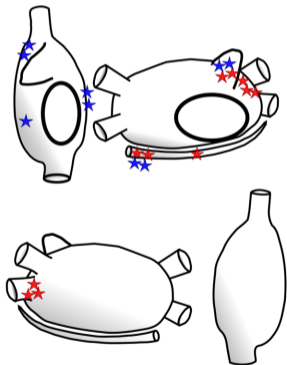


Anatomical macro-reentry



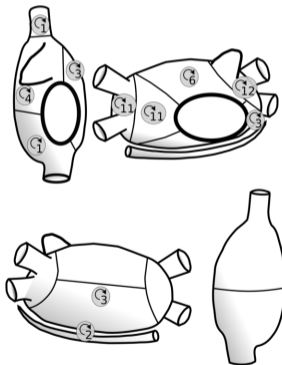
anatomical distribution

Focal AT



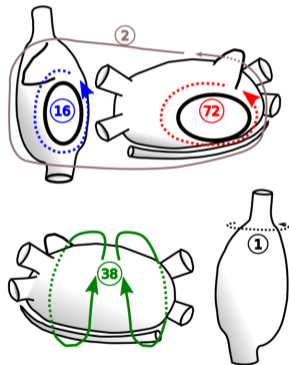
n=20

Scar-related localized reentry



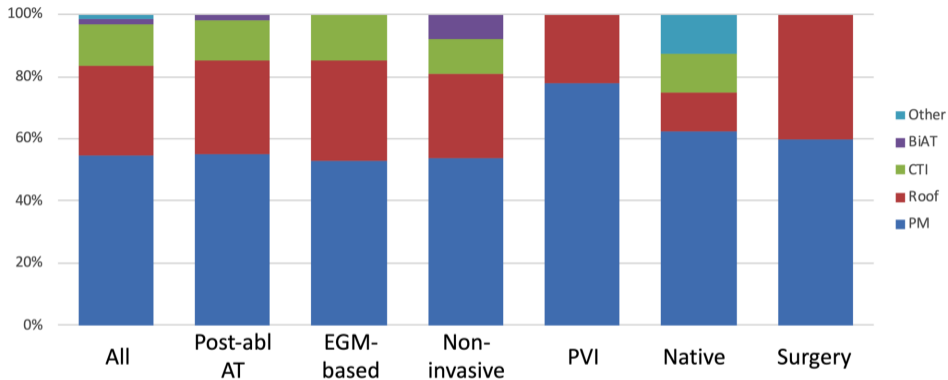
n=57

Macroreentry

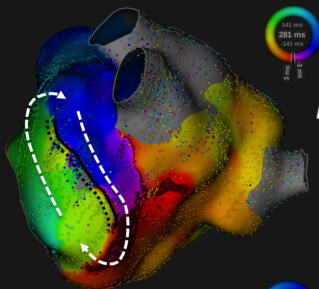


n=129

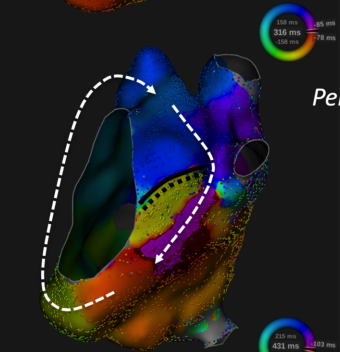
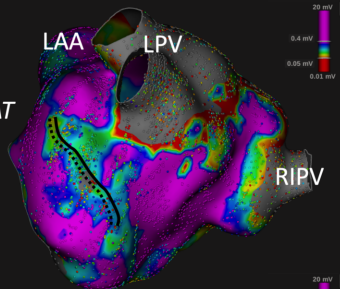
Distribution of type of macro-reentrant AT in each arrhythmia substrate



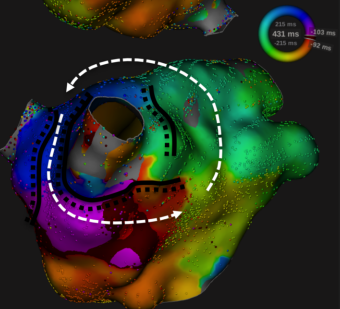
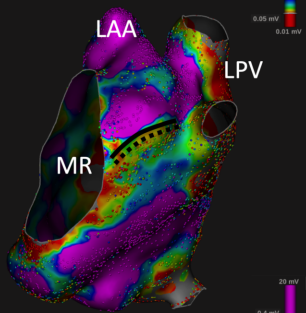
	PM (n)	PM (%)	Roof (n)	Roof (%)	CTI (n)	CTI (%)	BiAT (n)	BiAT (%)	Other (n)	Other (%)
Post Abl AT	64	55%	35	30%	15	13%	2	2%	0	0%
<i>EGM-based</i>	43	53%	26	32%	12	15%	0	0%	0	0%
<i>Non-invasive</i>	14	54%	7	27%	3	12%	0	0%	0	0%
<i>PVI</i>	7	78%	2	22%	0	0%	2	8%	0	0%
Native	5	63%	1	12%	1	12%	0	0%	1	12%
Surgery	3	60%	2	40%	0	0%	0	0%	0	0%
All	72	56%	38	29%	16	12%	2	2%	1	1%



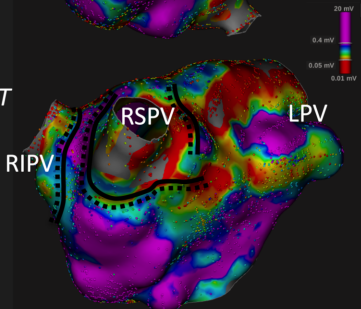
AT 1
Localized AT



AT 2
Perimitral AT

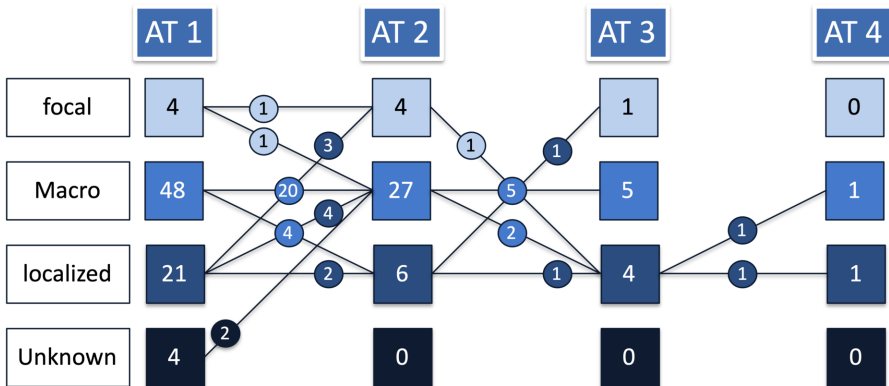
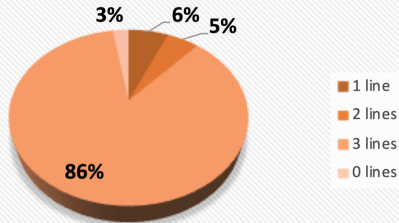


AT 2
Roof AT



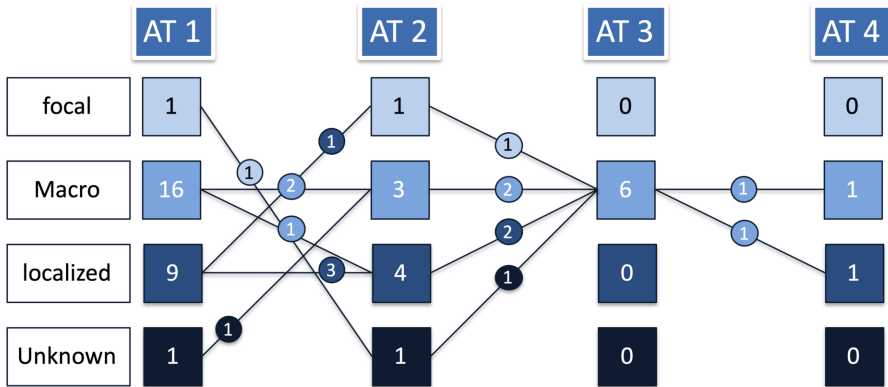
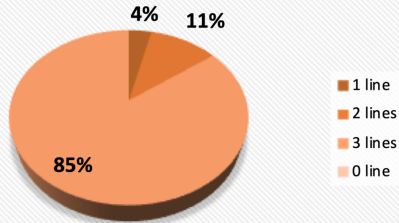
Initial persistent AF ablation strategy: EGM guided ablation

- 77 patients, 126 AT
- 1,6 AT/pts
- 3,1 procedures / pts
- 40 patients single AT
- 37 patients multiple AT



Initial persistent AF ablation strategy: ECGi guided ablation

- 27 patients, 44 AT
- 1,6 AT/pts
- 2,8 procedures / pts
- 18 patients single AT
- 9 patients multiple AT

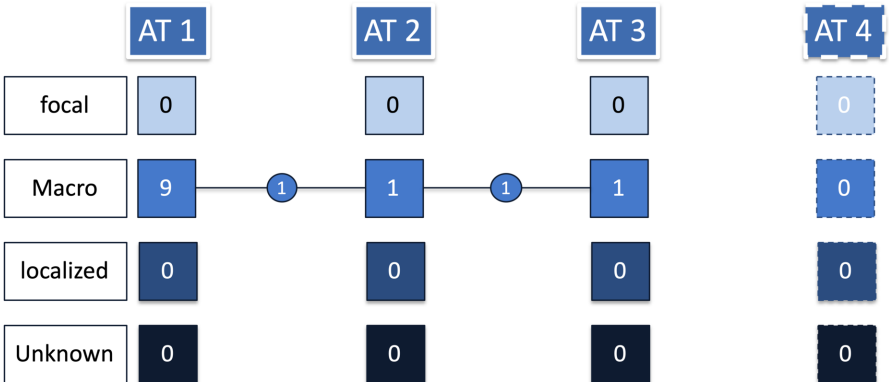


Initial persistent AF ablation strategy: PV isolation

- 8 patients, 9 AT
- 1,6 AT/pts
- 2,6 procedures / pts
- 8 patients single AT
- 1 patient multiple AT

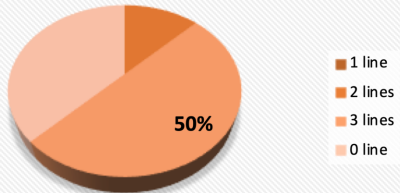


100%



Atrial Tachycardia in native atria

- 16 patients, 27 AT
- 1,7 AT/pts
- 1,5 procedures / pts
- 7 patients single AT
- 9 patient multiple AT



LA AT (n=8)

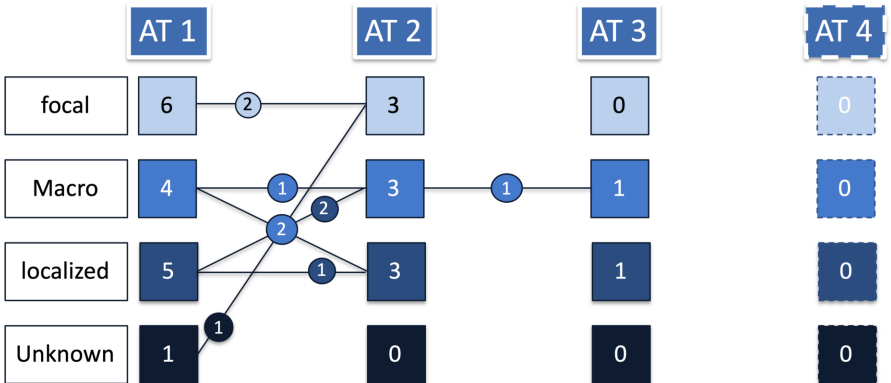


Table 1: Patients characteristics

Clinical Characteristics (n=132)	
Age, y	60±12
Female, n (%)	31 (23%)
LVEF, %	56±12
LA volume, cm ³	146±41
Hypertension, n (%)	48 (36%)
Diabetes mellitus, n (%)	5 (4%)
Stroke, n (%)	7 (5%)
CHA ₂ DS ₂ Vasc score	1.4±1.2
Structural Heart Disease, n (%)	33 (25%)
Atrial substrate	
<i>Post AF ablation, n (%)</i>	111 (84%)
<i>Post surgery, n (%)</i>	5 (4%)
<i>Native atria, n (%)</i>	16 (12%)
Number of ablation procedure/patient	2.7±1.3
Ablation strategy at index procedure in postAF ablation AT (n=111)	
PVI only	7 (6%)
PVI + stepwise ablation	77 (70%)
PVI + ECGi guided ablation	27 (24%)

Table 2: AT mechanisms distribution depending of atrial substrate

Substrate (pts/AT)	Focal		Localized		Macroreentry		Unknown	
	Pts	AT	Pts	AT	Pts	AT	Pts	AT
PostAF ablation (111/179)	10 (59%)	11 (55%)	37 (79%)	46 (80%)	83 (89%)	116 (90%)	7 (87%)	7 (87%)
<i>PV Isolation</i> (7/9)	0	0	0	0	7 (8%)	9 (8%)	0	0
<i>EGM-based</i> (77/126)	8 (80%)	9 (82%)	28 (74%)	32 (70%)	55 (66%)	81 (70%)	4 (57%)	4 (57%)
<i>Non-invasive</i> (27/44)	2 (20%)	2 (18%)	10 (26%)	14 (30%)	21 (25%)	26 (22%)	3 (43%)	3 (43%)
Native	7 (41%)	9 (45%)	8 (17%)	9 (16%)	6 (7%)	8 (6%)	0	0
Surgery	0	0	2 (4%)	2 (4%)	4 (4%)	5 (4%)	1 (13%)	1 (13%)
Total	17	20	47	57	93	129	8	8

Abbreviations: AT, atrial tachycardia; ECG, electrogram; Pts, patients; PV, pulmonary vein

Table 3: Mapping characteristics

Mapping characteristics (n=214)	
Left atria	
LA points, n	15 200±7683
LA volume, ml	147±41
LA mapping time, sec	924±484
LA mapping beats, n (%)	1 615±1294
Right atria	
RA mapping, n (%)	45 (21%)
RA points, n (%)	8 238±7 596
RA volume	114±81
RA mapping time, sec	601±534
RA mapping beats, n (%)	842±836
Reannotation, n (%)	22 (10%)
Mean reannotation points per map	6

Tables 4: Comparison of the characteristics of circuit and critical isthmus between the different type of atrial tachycardia

	Focal AT (FAT)	Localized AT (LAT)	Anatomical macro (MAT)	p- FAT vs. LAT	p- FAT vs. MAT	p- LAT vs. MAT
Critical isthmus						
/focal source						
Amplitude EGMs (mV)	0.65±0.60mV	0.20±0.22	0.43±0.68	0,119	0,002	0,045
Duration of EGMs (ms)	65,6±45,4	113,6±51,7	83,2±36,3	0,116	<0,001	<0,001
Fragmented EGms	55%	100%	73%	<0,001	<0,001	<0,001
Shortest length (mm)	-	11,8±7,2	15,2±9,3	-	-	0,014
% of AT cycle length	22±15%	39±17%	30±12%	0,058	0,001	<0,001
Circuit						
Diameter (mm)	-	25,8±12,2	44,2±9,6	-	-	0,014