Published in final edited form as:

Int J Cardiol. 2017 December 01; 248: 188–195. doi:10.1016/j.ijcard.2017.07.003.

Spatial relationship of sites for atrial fibrillation drivers and atrial tachycardia in patients with both arrhythmias

Tina Baykaner^{a,*}, Junaid A.B. Zaman^a, Albert J. Rogers^a, Rachita Navara^a, Mahmood AlHusseini^a, Ryan T. Borne^b, Shirley Park^a, Paul J. Wang^a, David E. Krummen^c, William H. Sauer^b, and Sanjiv M. Narayan^a

^aStanford University Medical Center, Palo Alto, CA, United States

^bUniversity of Colorado School of Medicine, Denver, CO, United States

^cUniversity of California San Diego and Veterans Affairs Medical Center, La Jolla, CA, United States

Abstract

Introduction—Atrial fibrillation (AF) often converts to and from atrial tachycardia (AT), but it is undefined if these rhythms are mechanistically related in such patients. We tested the hypothesis that critical sites for AT may be related to regional AF sources in patients with both rhythms, by mapping their locations and response to ablation on transitions to and from AF.

Methods—From 219 patients undergoing spatial mapping of AF prior to ablation at 3 centers, we enrolled 26 patients in whom AF converted to AT by ablation ($n = 19$) or spontaneously ($n = 7$; left atrial size 42 ± 6 cm, 38% persistent AF). Both atria were mapped in both rhythms by 64-electrode baskets, traditional activation maps and entrainment.

Results—Each patient had a single mapped AT (17 reentrant, 9 focal) and 3.7 ± 1.7 AF sources. The mapped AT spatially overlapped one AF source in 88% (23/26) of patients, in left (15/23) or right (8/23) atria. AF transitioned to AT by 3 mechanisms: (a) ablation anchoring AF rotor to AT ($n = 13$); (b) residual, unablated AF source producing AT ($n = 6$); (c) spontaneous slowing of AF rotor leaving reentrant AT at this site without any ablation ($n = 7$). Electrogram analysis revealed a lower peak-to-peak voltage at overlapping sites (0.36 ± 0.2 mV vs 0.49 ± 0.2 mV $p = 0.03$).

Conclusions—Mechanisms responsible for AT and AF may arise in overlapping atrial regions. This mechanistic inter-relationship may reflect structural and/or functional properties in either atrium. Future work should delineate how acceleration of an organized AT may produce AF, and whether such regions can be targeted a priori to prevent AT recurrence post AF ablation.

*Corresponding author at: Stanford University, 780 Welch Road MC 5773, Palo Alto, CA 94305, United States. tina4@stanford.edu (T. Baykaner).

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.ijcard.2017.07.003>.

Author contributions

T.B.: data collection, drafting article, statistics, data analysis/interpretation; A.J.R., R.N.: data collection; M.A., R.T.B., J.A.B.Z.: data analysis/interpretation; S.P., P.J.W., D.E.K., W.S.: critical revision of article; S.M.N.: concept/design, critical revision of article.

Keywords

Atrial tachycardia; Atrial fibrillation; Rotors; Phase mapping; Localized sources; Voltage

1. Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia in the world and a leading cause of hospitalization and death [1]. AF frequently coexists with atrial tachycardias (AT) in patients without a history of ablation [2,3], but for unclear mechanisms. AT is also a common form of recurrence following an AF ablation procedure [1] which is often attributed to gaps in linear ablation lesions. However, clinical experience shows that AT may result acutely even from focused AF ablation without lines [4–6] or later in follow-up. Defining mechanisms by which AF and AT transition may shed light on ablatable mechanisms to reduce post-AF ablation arrhythmias.

We hypothesized that in patients with transitions to/from AF and AT, both arrhythmias may be mechanistically related to overlapping regions, for instance reentrant or focal AT may accelerate or combine with additional asynchronous mechanisms to produce fibrillatory conduction and AF. This follows several lines of reasoning. First, optical mapping studies of human atria ex vivo reveal stable endocardial micro-reentrant sources for AF, where localized ablation resulted in AT from these sites [7] as we have reported [8]. Second, focal impulse and rotor mapping (FIRM) of clinical AF reveals rotational and focal sources (in $\approx 2\text{--}3\text{ cm}^2$ areas) [4], similar to human optical mapping [7], where localized ablation terminates AF to AT as reported clinically by many groups [5,9–12]. Third, the ability of localized ablation at AF sources to acutely terminate AF to AT supports the localized source model of AF [13,14]. Finally, clinical ablation of AF may coincidentally hit localized sources and explain frequent observed conversions to AT prior to complete isolation of PVs or complete linear lesions [4].

We tested our hypothesis in patients with interconverting AF and AT, by defining for each arrhythmia their mechanism, locations and response to ablation. We used several strategies to clarify mechanisms, including electroanatomic mapping, FIRM-mapping and entrainment mapping of AT, FIRM-mapping of AF and voltage mapping of atrial substrates.

2. Methods

2.1. Clinical recruitment

From 219 patients with AF undergoing ablation at University of California, San Diego, Stanford University and the University of Colorado, we identified 26 patients in whom AF transitioned to AT spontaneously ($n = 7$) or by ablation ($n = 19$). We did not include cases where AT's terminated or reconverted to AF before mechanisms could be clarified by activation mapping, entrainment mapping, FIRM mapping or AT ablation. Patients provided written informed consent and were studied according to the Institutional Review Board of these centers.

2.2. Electrophysiological study

Patients discontinued anti-arrhythmic medications for >5 half-lives except amiodarone. Heparin was used to maintain activated clotting time >350 s. A 64-pole basket catheter was advanced to the right atrium (RA), then trans-septally to left atrium (LA), avoiding errors in basket placement in recent studies [15]. The scale of predicted human AF circuits [16] (>1 cm²) was recently supported by human optical mapping [7,17] rendering them potentially amenable to mapping by clinical baskets. Electrode locations were referenced to electroanatomic shells (NavX, St Jude Medical, or Carto, Biosense-Webster). Patients presented in AF (n = 12) or AF was induced with pacing with >10 min to physiologically stabilize before mapping. Induced AF is spectrally and spatially similar to spontaneous AF [18]. Electrograms were filtered at 0.05–500 Hz and digitized at 1 kHz.

2.3. Atrial fibrillation (substrate) mapping

FIRM maps identify electrical rotors as phase singularities with surrounding disorganization. FIRM mapping employs algorithms to map propagation sequences from observed AF activations. For unipolar deflections, points of maximum negative dV/dt indicate each activation cycle in AF and can be used to identify AF rotational circuits as shown in Fig. 1B. If AF deflections are multiphasic and complex, classical rules can often identify multiple deflections of which some are far-field (i.e. within repolarization) which can affect mapping. FIRM determines local activation using rate-dependent conduction and repolarization [19,20], rather than assuming refractoriness, with phase analysis to clarify rotational patterns. Activation times are not interpolated or inserted, so that regions where no signal is detected remain black. FIRM mapped rotors show similarities to micro-reentrant drivers in optical mapping of AF in human atria [7], with concordance on simultaneous mapping in human hearts [21].

Rotors were considered AF sources if they were stable within 1–2 cm² for multiple recording epochs over 2–5 min. Focal AF sources were defined as origins with centrifugal activation and breakdown into meandering wavelets.

2.4. Mapping and definitions of atrial tachycardia/flutter

Atrial tachycardia/flutter was mapped using traditional electrogram and entrainment criteria and electroanatomic mapping; FIRM mapping was used to correlate with regional sites of AF organization.

Organized AT was diagnosed, distinct from AF, by a reproducible activation sequence in coronary sinus and other basket catheter electrodes, consistent electrogram shape and, if discernible, consistent f/p-wave shape on ECG. Reentrant AT was confirmed by entrainment, focal AT by intra-atrial activation spanning <70% of tachycardia cycle length, and reentry from a spiral activation sequence. Successful ablation was used to confirm the diagnosis of AT.

2.5. Definition of overlapping atrial regions causing AT and AF

AF drivers were mapped, marked on electroanatomic shells, and then ablated. The spatial relationship of these sites was correlated to multipolar basket electrodes in the atrium and

anatomic structures such as the pulmonary veins and the atrial appendage. In general, the mapped location of each localized AT was marked and ablated in a rosette lesion set of approximately 2cm² on the electroanatomic shell. The location of AT sites were also correlated to multipolar electrodes and anatomic structures. In each patient, regions of AT or AF mechanisms were considered shared if they lay within ± 1 cm on electroanatomic shells [22] on blinded analysis. In each patient, regions of AT or AF sources were considered shared if they lay within ± 1 cm on electroanatomic shells [22] on blinded analysis.

2.6. Additional characterization of atrial substrates

Voltage was quantified globally biatrially using unipolar electrograms from basket catheters. In AF, unipolar voltages were analyzed simultaneously at all basket poles prior to any ablation in semi-automated fashion using customized software in *Labview* (National Instruments, TX). These voltages were depicted as a heat map of peak-to-peak voltages reflecting the locations of AF and AT mechanisms.

2.7. Ablation of AT or AF

AF ablation commenced with FIRM-guided radiofrequency ablation, using a 3.5 mm tip irrigated (Biosense-Webster), or non-irrigated (Boston Scientific) catheter in cases of heart failure. Ablation was delivered to the organized rotor domain (areas of 2–3 cm² as confirmed in human optical maps [7]). Ablation was performed at right then left atrial sites, and repeated to eliminate rotors on remapping. Ablation lesions at AF drivers were marked on electroanatomic shells. Ablation typically concluded with PVI, via wide-area circumferential ablation (WACA). The use of adenosine or other maneuvers were operator-dependent. A minority of patients requested FIRM-only ablation without PVI under specific IRB-approved protocols.

All AT's were mapped and ablated if sustained or previously clinically relevant. Sustained AT's lasting >2 min were ablated by either interrupting a macro-reentrant circuit with an interposed line of block connecting electrically inert tissue, or by focal ablation as indicated.

2.8. Follow-up

Treatment varied between patients, and follow-up is not the primary aim of this mechanistic study. However, after a 3-month blanking period, anti-arrhythmic medications were discontinued and AF or AT recurrences were detected using periodic ambulatory ECGs, unscheduled ECGs for symptoms, or implanted ECG monitors when possible.

2.9. Statistical analysis

Continuous variables were presented as mean $\pm$ standard deviation (SD). The two-tailed *t*-test was used to compare continuous variables between groups. Because of the small sample sizes, exact confidence limits for sensitivity and specificity were computed using binomial probabilities. A paired-sample *t*-test was used to determine whether any difference between the average voltage at AT sites and the remaining atrium was statistically significant. Nominal values are expressed as n (%) and compared with Chi² tests or Fisher exact test when expected cell frequency was <5. Probabilities below 5% ($p < 0.05$) were considered significant.

3. Results

3.1. Demographics

Table 1 summarizes patient characteristics and the ablation performed in each case. This study includes $n = 26$ patients with mapped AF and AT, and involved quantitative analysis of 3328 electrogram channels.

3.2. Conversions from atrial fibrillation to and from atrial tachycardia

Each patient showed transitions between AF and AT, either by FIRM-guided ablation that converted AF to AT before PV isolation ($n = 19$) or spontaneously before any ablation ($n = 7$).

Fig. 1 illustrates AF in a 60 year old man with persistent AF, with organized rotational drivers where ablation anchored AF to reentrant AT anchored at that site. Fig. 1A shows the transition from AF to AT. In AF, FIRM maps show rotational organization in the posterior LA during AF (Fig. 1B, left). Fig. 1C shows the electroanatomic shell and ablation lesions at this site. <1 min of ablation at this site transitioned AF to AT, demonstrated in the right panel of Fig. 1B. Notably, the AT reentry circuit neighbors the rotational AF site, but with longer cycle length. Pacing in the left atrium during AT showed entrainment, with concealed fusion when pacing at the left atrial AT reentrant site (Supplemental Fig. 1). Continued ablation at this site terminated AT to sinus rhythm. The patient subsequently underwent PVI. AT recurred on day 108, and mapping showed the same posterior LA AT from incomplete ablation, that was successfully ablated. The patient remains free of AF/AT at 3 years post-ablation.

Fig. 2 shows a case of AF in a 43 year old man with paroxysmal AF, in which several AF sources were identified at all but one was eliminated by ablation. Once the final source was remaining, the rhythm converted to AT arising from that residual AF source. This was seen in 6 patients.

Fig. 3 shows spontaneous conversion of AF to AT, in parallel with slowing of the AF source and loss of peripheral disorganized activation. Fig. 3A shows electrograms in AF (left), and during spontaneous organization to AT (right; CL 206 ms). Fig. 3B shows a LA FIRM map of AF, with a rotational circuit in the posterior LA (CL ≈ 140 ms). Spontaneous AT (Fig. 3B, right panel) shows slower reentry (CL 206 ms). AF and AT circuits lay within 1 cm on NavX shell (Fig. 3C). Ablation at this shared atrial site in AF produced sinus rhythm. PVI was not performed (under IRB-protocol); the patient has been free of AF/AT at 1 year follow-up.

Fig. 4 shows another example of spontaneous conversion of AF to AT. Mapping demonstrated that AF was driven by a concurrent lateral RA rotational source and septal focal source (Fig. 4A–B). Mapping after spontaneous conversion of AF to AT showed a focal source at the shared atrial site in the septal RA (Fig. 4C).

3.3. Mechanisms of atrial fibrillation – atrial tachycardia conversions

Biatrial mapping revealed 3.7 ± 1.7 sources for AF, in left (64.6%) or right (35.4%) atrium surrounded by disordered activation. AT in each patient was caused by reentrant mechanisms ($n = 17$) or focal sources ($n = 9$), with 17 in LA and 9 in RA (including 1 case of reverse typical atrial flutter). Of all AF/AT interconversions, 88% (23/26) reflected shared atrial regions in left (15/23) or right (8/23) atria at locations shown in Fig. 5.

Three mechanisms were identified. In the first, AT arose when ablation anchored an AF rotor into the anatomic site of reentrant AT (Fig. 1). This mechanism was seen in $n = 13$ cases, associated with CL prolongation from 183 ± 10 ms (AF) to 250 ± 26 ms (AT; $p < 0.01$). In the second mechanism, AT arose at a residual AF source after others were ablated ($n = 6$ cases), associated with CL prolongation from 180 ± 11 ms (AF) to 232 ± 55 ms (AT; $p = \text{NS}$). Lastly, spontaneous slowing of AF rotor/focal sources increased their spatial domain to ultimately activate all atrial regions 1:1 (i.e. AT). In Fig. 3, overlapping regions of posterolateral left atrium were mechanistically related to AT and AF as subsequently confirmed by ablation causing termination to sinus rhythm, and lack of AT or AF recurrence on follow-up. This mechanism explained $n = 7$ transitions before any ablation, associated with CL prolongation from 180 ± 12 ms (AF) to 228 ± 27 ms (AT; $p = 0.02$).

3.4. Substrate characteristics of shared sites

Sites of overlapping AF/AT drivers had lower voltage than the remaining atrium (0.36 ± 0.2 vs 0.49 ± 0.2 mV $p = 0.03$). Fig. 4D illustrates atrial voltage in a heat map, in which the AF/AT region had lower voltage (red) than surrounding regions. Voltages did not differ between right and left atria for shared AF/AT regions (0.32 ± 0.20 vs 0.39 ± 0.30 mV; $p = \text{NS}$) or non-driver atrial sites (0.49 ± 0.20 mV vs. 0.48 ± 0.20 mV; $p = \text{NS}$).

4. Discussion

This study is one of the first to examine the mechanistic interplay between AT and AF in patients with both arrhythmias. In this multicenter series of patients undergoing AF ablation who had concurrent AT, we found substantial spatial overlap between localized AF sources and AT locations in left and right atria. We identified three mechanisms for conversions of AF to AT. First, cases in which ablation of AF rotational drivers anchored a reentrant AT. Second, cases in which AT arose from a residual AF source after eliminating other sources. Third, cases in which spontaneous slowing of a localized AF driver reduced peripheral disorder enabling it to capture both atria 1:1. Clinically, AT recurrence after AF ablation may therefore represent intrinsic rather than iatrogenic mechanisms in some cases, motivating approaches to identify these sites a priori. Mechanistically, these findings further emphasize the role of localized structural or functional abnormalities in producing diverse atrial arrhythmias.

4.1. Is human AF maintained by localized rotational or focal sources?

These data add to evidence [23] that human AF is maintained by localized sources, although debate continues. Recent optical mapping studies of human atria show stable drivers for AF on the endocardium, that appear unstable on the epicardium explaining data from ECG

methods [6], where localized endocardial ablation terminated AF to AT or sinus rhythm [7]. Further studies show that micro-reentrant sources in AF are indeed detected by FIRM in human atria [7].

These data are also consistent with the clinical efficacy of ablating rotors and focal sources, shown in the CONFIRM trial [4] and confirmed by Sommer et al. in patients with longstanding persistent AF [24], Miller et al. [9,12], Tomassoni et al. [11] and others [10]. Disappointing long term outcomes from some centers [25] may reflect procedural issues [15] or small series. It is notable that even studies with disappointing long-term results showed acute conversion of AF to AT in 34% of cases by FIRM-guided ablation alone [26], supporting the role of these sites in driving the fibrillatory process. In at least one study, AT resulting from FIRM-guided ablation of AF were not ablated and contributed to long-term AT recurrence. In terms of technical limitations, in one study [15] nearly half of recorded sites had atrial CL $\approx$ 250–500 ms (dominant frequency 2–4 Hz) [15] questioning their recordings of AF, while other studies mapped small regions which may miss AF sources [13]. Further work should continue to compare electrogram-based with optical mapping.

4.2. Are AF and AT a spectrum of the same disease?

AT or atrial flutter commonly arise in AF patients, with and without ablation [2,5,27]. The high incidence of AF in patients with lone atrial flutter is well known [3], and AF ablation at the time of CTI-dependent atrial flutter ablation reduces the incidence of AF [28]. Nevertheless, few studies have identified mechanisms for how CTI-dependent flutter relate to AF. Similarly, non-CTI-dependent (atypical) flutters may convert to and from AF [2], yet are poorly explained.

We present three mechanisms to explain inter-conversions between AF and AT in individual patients. First, ablation of a localized AF rotor can anchor it to AT as we reported computationally [8] (Fig. 1). Second, elimination of AF sources can leave AT as a residual, unablated AF source (Fig. 2). Third, deceleration of an AF rotor reduces fibrillatory conduction and may result in AT (Fig. 3). Causes for deceleration are unclear, but may reflect prolonged repolarization from changes in autonomic balance, metabolic factors or loading conditions. We illustrate cases in whom these mechanisms explained conversion of AF to and from atypical AT (Figs. 1, 3), typical flutter (Fig. 2) and focal AT (Fig. 4).

These results expand early work from our laboratory and others, using spectral and spatial analyses [29] to demonstrate that AT and AF lie at two ends of an organizational spectrum. Our results differ somewhat from the work of Yoshida et al., who suggest that AT continues at a slow rate during AF (a low frequency peak during high frequency AF [30]), while we show that the same tissue region may drive AT when relatively slow, and AF when it accelerates.

4.3. Does AT arise from prior ablation or spontaneously in AF patients?

Several studies show that AF ablation may produce AT [31], but the extent of ablation in those studies has confused mechanistic debate. While AT may clearly arise at gaps in ablation sets in some patients, particularly after extensive procedures, this does not explain conversions of AF to AT spontaneously [2,3], or by limited ablation as in this study. Our

ablation strategy was conservative, performed prior to PVI in this study, and we did not perform linear or extensive stepwise or complex fractionated electrogram ablation. This may explain the distribution of atrial tachycardias in these patients compared to prior studies.

Our data suggest that AT recurrences after AF ablation may also result from partial elimination of AF rotors/focal sources, as a roof line or WACA may coincidentally eliminate AF sources [4]. In this series we show that partially-ablated AF sources may cause recurrent AT (Fig. 1). It is also possible that ablation near the core of a reentrant AF driver may have ‘pinned’ the driver and actually resulted in atrial tachycardia [8]. Elegant optical mapping of human atria recently revealed concurrent AF drivers [17], although the impact of an unablated rotor was not studied. Ablation studies should use continuous mapping to define such mechanisms and potentially target such sources.

4.4. Potential substrate characteristics of shared AF/AT mechanisms

Recent translational and clinical MRI studies suggest that atrial fibrosis can play an important role in the maintenance of AF by causing disorganized activity or anchoring rotors [1,23]. Areas of fibrosis demonstrated with cardiac MRI are closely associated with low voltage areas measured during EP studies [32]. Our exploratory analysis showing lower voltage at shared sites for AF/AT is consistent with such associations, but requires further validation.

5. Limitations

Whilst the very role of rotors in human AF is currently debated, this study uses the controversy as an advantage by re-emphasizing the ability of localized ablation at AF sources to acutely produce AT, as reported by studies of FIRM with good [9,10,12,24] as well as disappointing [5,25] outcomes. These frequent clinical observations are difficult to explain by disorganized models of AF [13,14]. This study was small in size; studies in larger populations are underway. Brief periods of organization from AF to other AT may not have been captured in this study. Nevertheless, each case in this series had at least one interconversion between AF and AT. Inclusion of induced AF can be criticized, but this enabled the study of conversions from paroxysmal AF to AT. Once induced, even paroxysmal AF can sustain for prolonged periods and is often not terminated by PV isolation [1].

6. Conclusions

Our data show that AT and AF sites may reflect shared mechanisms in either atrium, which may reflect structural substrates. These data provide a potential unifying mechanism for the commonly observed association between spontaneous AF and AT, and between ablated AF and recurrent AT. They also strengthen the mechanistic role of AF rotational and focal drivers, given that ablation of <2–3% of atrial area is unlikely to terminate AF to AT if AF is due to disordered wavelets without preferred source regions. Future studies should examine how dynamic mechanisms enable organized circuits to produce the disorganized AF phenotype, and explore whether these sites can be identified a priori.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Author disclosure information

T. B., J.A.B.Z., A.J.R., R.N., M.A., R.T.B., S.P.: None; P.J.W.: Compensation for Services from Medtronic, Inc., St. Jude Medical, Janssen Pharmaceuticals. Research Grants from Medtronic, Inc., CardioFocus, Inc., Fellowship Support from Medtronic, Inc., St. Jude Medical, Boston Scientific Corp., Biosense Webster, Inc.; D.E.K.: Research Grants from NIH; University of California Regents. Fellowship Support from Biosense Webster, Inc., Biotronik, Boston Scientific Corp., Medtronic, Inc., St. Jude Medical; W.H.S.: Compensation for Services from CardioNXT, Biosense Webster, Inc., Boston Scientific Corp., Equity Interests/Stock Options from CardioNXT. Research Grants from Biosense Webster, Inc.; S.M.N.: Compensation for Services from Up to Date, Abbott Laboratories, American College of Cardiology Foundation. Speaking/consulting fees from Medtronic, Inc., St. Jude Medical. Equity Interests from Topera Medical. Research Grants from National Institutes for Health. Intellectual Property Rights from University of California Regents.

Abbreviations

AF	atrial fibrillation
AT	atrial tachycardia
CL	cycle length
CTI	cavo-tricuspid isthmus
DCCV	direct current cardioversion
FIRM	focal impulse and rotor modulation
LA	left atrium
PVI	pulmonary vein isolation
RA	right atrium
WACA	wide area circumferential ablation

References

1. Calkins CH. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. *Heart Rhythm*. 2012; 9:632–696. [PubMed: 22386883]
2. Yang Y, Mangat I, Glatter KA, Cheng J, Scheinman MM. Mechanism of conversion of atypical right atrial flutter to atrial fibrillation. *Am J Cardiol*. 2003; 91:46–52. [PubMed: 12505570]
3. Halligan SC, Gersh BJ, Brown RD Jr, Rosales AG, Munger TM, Shen W-K, Hammill SC, Friedman PA. The natural history of lone atrial flutter. *Ann Intern Med*. 2004; 140:265–268. [PubMed: 14970149]
4. Narayan SM, Baykaner T, Clopton P, Schricker A, Lalani GG, Krummen DE, Shivkumar K, Miller JM. Ablation of rotor and focal sources reduces late recurrence of atrial fibrillation compared with trigger ablation alone: extended follow-up of the CONFIRM trial (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation). *J Am Coll Cardiol*. 2014; 63:1761–1768. [PubMed: 24632280]

5. Shivkumar K, Ellenbogen KA, Hummel JD, Miller JM, Steinberg JS. Acute termination of human atrial fibrillation by identification and catheter ablation of localized rotors and sources: first multicenter experience of focal impulse and rotor modulation (FIRM) ablation. *J Cardiovasc Electrophysiol.* 2012; 23:1277–1285. [PubMed: 23130890]
6. Haissaguerre M, Hocini M, Denis A, Shah AJ, Komatsu Y, Yamashita S, Daly M, Amraoui S, Zellerhoff S, Picat MQ, Quotb A, Jesel L, Lim H, Ploux S, Bordachar P, Attuel G, Meillet V, Ritter P, Derval N, Sacher F, Bernus O, Cochet H, Jais P, Dubois R. Driver domains in persistent atrial fibrillation. *Circulation.* 2014; 130:530–538. [PubMed: 25028391]
7. Hansen BJ, Zhao J, Csepe TA, Moore BT, Li N, Jayne LA, Kalyanasundaram A, Lim P, Bratasz A, Powell KA, Simonetti OP, Higgins RS, Kilic A, Mohler PJ, Janssen PM, Weiss R, Hummel JD, Fedorov VV. Atrial fibrillation driven by micro-anatomic intramural re-entry revealed by simultaneous sub-epicardial and sub-endocardial optical mapping in explanted human hearts. *Eur Heart J.* 2015; 36:2390–2401. [PubMed: 26059724]
8. Rappel WJ, Zaman JA, Narayan SM. Mechanisms for the termination of atrial fibrillation by localized ablation: computational and clinical studies. *Circ Arrhythm Electrophysiol.* 2015; 8:1325–1333. [PubMed: 26359479]
9. Miller JM, Kowal RC, Swarup V, Daubert JP, Daoud EG, Day JD, Ellenbogen KA, Hummel JD, Baykaner T, Krummen DE, Narayan SM, Reddy VY, Shivkumar K, Steinberg JS, Wheelan KR. Initial independent outcomes from focal impulse and rotor modulation ablation for atrial fibrillation: multicenter FIRM registry. *J Cardiovasc Electrophysiol.* 2014; 25:921–929. [PubMed: 24948520]
10. Rashid H, Sweeney A. Approaches for focal impulse and rotor mapping in complex patients: a US private practice perspective. *J Innov Card Rhythm Manag.* 2015; 6:2193–2198.
11. Tomassoni G, Duggal S, Muir M, Hutchins L, Turner K, McLoney AM, Hesselson A. Long-term follow-up of FIRM-guided ablation of atrial fibrillation: a single-center experience. *J Innov Card Rhythm Manag.* 2015; 6:2145–2151.
12. Miller JM, Kalra V, Mithilesh DK, Jain R, Garlie JB, Brewster JA, Gopi D. Clinical benefit of ablating localized sources for human atrial fibrillation: the Indiana University FIRM Registry. *J Am Coll Cardiol.* 2017; 69 Epub.
13. Allesie MA, de Groot NM, Houben RP, Schotten U, Boersma E, Smeets JL, Crijns HJ. Electropathological substrate of long-standing persistent atrial fibrillation in patients with structural heart disease: longitudinal dissociation. *Circ Arrhythm Electrophysiol.* 2010; 3:606–615. [PubMed: 20719881]
14. Lee S, Sahadevan J, Khrestian CM, Cakulev I, Markowitz A, Waldo AL. Simultaneous biatrial high-density (510–512 electrodes) epicardial mapping of persistent and long-standing persistent atrial fibrillation in patients: new insights into the mechanism of its maintenance. *Circulation.* 2015; 132:2108–2117. [PubMed: 26499963]
15. Jalife J, Filgueiras Rama D, Berenfeld O. Letter by Jalife et al regarding article, “quantitative analysis of localized sources identified by focal impulse and rotor modulation mapping in atrial fibrillation”. *Circ Arrhythm Electrophysiol.* 2015; 8:1296–1298. [PubMed: 26487627]
16. Rensma P, Allesie M, Lammers W, Bonke F, Schalij M. Length of excitation wave and susceptibility to reentrant atrial arrhythmias in normal conscious dogs. *Circ Res.* 1988; 62:395–410. [PubMed: 3338122]
17. Zhao J, Hansen BJ, Csepe TA, Lim P, Wang Y, Williams M, Mohler PJ, Janssen PM, Weiss R, Hummel JD, Fedorov VV. Integration of high-resolution optical mapping and 3-dimensional micro-computed tomographic imaging to resolve the structural basis of atrial conduction in the human heart. *Circ Arrhythm Electrophysiol.* 2015; 8:1514–1517. [PubMed: 26671938]
18. Calvo D, Atienza F, Jalife J, Martinez-Alzamora N, Bravo L, Almendral J, Gonzalez-Torrecilla E, Arenal A, Bermejo J, Fernandez-Aviles F, Berenfeld O. High-rate pacing-induced atrial fibrillation effectively reveals properties of spontaneously occurring paroxysmal atrial fibrillation in humans. *Europace.* 2012; 14:1560–1566. [PubMed: 22696516]
19. Narayan SM, Wright M, Derval N, Jadidi A, Forclaz A, Nault I, Miyazaki S, Sacher F, Bordachar P, Clementy J, Jais P, Haissaguerre M, Hocini M. Classifying fractionated electrograms in human atrial fibrillation using monophasic action potentials and activation mapping: evidence for localized drivers, rate acceleration and non-local signal etiologies. *Heart Rhythm.* 2011; 8:244–253. [PubMed: 20955820]

20. Narayan SM, Franz MR, Clopton P, Pruvot EJ, Krummen DE. Repolarization alternans reveals vulnerability to human atrial fibrillation. *Circulation*. 2011; 123:2922–2930. [PubMed: 21646498]
21. Hansen BJ, Briggs C, Moore BT, Csepe TA, Li N, Zhao J, Garikipati NV, Janssen PM, Mohler PJ, Hummel JD, Fedorov VV. Human atrial fibrillation drivers seen simultaneously by focal impulse and rotor mapping and high-resolution optical mapping [abstract]. *Circulation*. 2015; 132:A18402.
22. Lalani GG, Coysh T, Baykaner T, Zaman J, Hopper K, Schricker AA, Trikha R, Clopton P, Krummen DE, Narayan SM. Organized sources are spatially conserved in recurrent compared to pre-ablation atrial fibrillation: further evidence for nonrandom electrical substrates. *J Cardiovasc Electrophysiol*. 2016; 27:661–669. [PubMed: 26918971]
23. Pandit SV, Jalife J. Rotors and the dynamics of cardiac fibrillation. *Circ Res*. 2013; 112:849–862. [PubMed: 23449547]
24. Sommer P, Kircher S, Rolf S, John S, Arya A, Dinov B, Richter S, Bollmann A, Hindricks G. Successful repeat catheter ablation of recurrent longstanding persistent atrial fibrillation with rotor elimination as the procedural endpoint: a case series. *J Cardiovasc Electrophysiol*. 2016; 27:274–280. [PubMed: 26527103]
25. Buch E, Share M, Tung R, Benharash P, Sharma P, Koneru J, Mandapati R, Ellenbogen KA, Shivkumar K. Long-term clinical outcomes of focal impulse and rotor modulation for treatment of atrial fibrillation: a multicenter experience. *Heart Rhythm*. 2015; 13:636–641. [PubMed: 26498260]
26. Gianni C, Mohanty S, Di Biase L, Metz T, Trivedi C, Gokoglan Y, Gunes MF, Bai R, Al-Ahmad A, David Burkhardt J, Joseph Gallinghouse G, Horton R, Hranitzky PM, Sanchez JE, Halbfass P, Muller P, Schade A, Deneke T, Tomassoni GF, Natale A. Acute and early outcomes of FIRM-guided rotors-only ablation in patients with non-paroxysmal atrial fibrillation. *Heart Rhythm*. 2016; 13:830–835. [PubMed: 26706193]
27. Hsieh MH, Tai CT, Chiang CE, Tsai CF, Yu WC, Chen YJ, Ding YA, Chen SA. Re-current atrial flutter and atrial fibrillation after catheter ablation of the cavotricuspid isthmus: a very long-term follow-up of 333 patients. *J Interv Card Electrophysiol*. 2002; 7(3):225–231. [PubMed: 12510133]
28. Steinberg JS, Romanov A, Musat D, Preminger M, Bayramova S, Artyomenko S, Shabanov V, Losik D, Karasov A, Shaw RE, Pokushalov E. Prophylactic pulmonary vein isolation during isthmus ablation for atrial flutter: the PREVENT AF Study I. *Heart Rhythm*. 2014; 11:1567–1572. [PubMed: 24832767]
29. Narayan SM, Bhargava V. Temporal and spatial phase analyses of the electrocardiogram stratifies intra-atrial and intra-ventricular organization. *IEEE Trans Biomed Eng*. 2004; 51:1749–1764. [PubMed: 15490822]
30. Yoshida K, Chugh A, Ulfarsson M, Good E, Kuhne M, Crawford T, Sarrazin JF, Chalfoun N, Wells D, Boonyapisit W, Veerareddy S, Billakanty S, Wong WS, Jongnarangsin K, Pelosi F Jr, Bogun F, Morady F, Oral H. Relationship between the spectral characteristics of atrial fibrillation and atrial tachycardias that occur after catheter ablation of atrial fibrillation. *Heart Rhythm*. 2009; 6:11–17. [PubMed: 19121795]
31. Haissaguerre M, Hocini M, Sanders P, Sacher F, Rotter M, Takahashi Y, Rostock T, Hsu LF, Bordachar P, Reuter S, Roudaut R, Clementy J, Jais P. Catheter ablation of long-lasting persistent atrial fibrillation: clinical outcome and mechanisms of subsequent arrhythmias. *J Cardiovasc Electrophysiol*. 2005; 16:1138–1147. [PubMed: 16302893]
32. Spragg DD, Khurram I, Zimmerman SL, Yarmohammadi H, Barcelon B, Needleman M, Edwards D, Marine JE, Calkins H, Nazarian S. Initial experience with magnetic resonance imaging of atrial scar and co-registration with electroanatomic voltage mapping during atrial fibrillation: success and limitations. *Heart Rhythm*. 2012; 9:2003–2009. [PubMed: 23000671]

Fig. 1.

Ablation at AF Rotor Anchors Activation to Reentrant AT in 60 year old man with persistent AF. A: ECG and CS electrograms demonstrating AF-AT transition. B: Left atrial FIRM maps of AF in left, showing posterior LA rotor with disorganization; AT in right, showing reentrant source at the AF rotor site with corresponding basket electrograms around the rotor core and AT source showing sequential activation (red lines) determined by minimum negative slope of dV/dt (green lines). C: NavX shell of the left atrium showing targeted AF rotor and AT site with eventual termination to sinus rhythm after ablation at this site. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fig. 2.

Successive Ablation of AF Rotors leaves AT at remaining AF Source in 43 year old man with paroxysmal AF. A: ECG and CS electrograms demonstrating AF-AT transition. B: On the left panel, FIRM in AF shows 2 LA rotors (posteroinferior and anterolateral) and intermittent rotation in RA. On the right panel, FIRM map of AT, consistent with the unablated RA site, confirmed to be CTI-dependent flutter. C: NavX map showing targeted LA rotor (lesions) causing transition to AT (3 min total ablation).

Fig. 3.

Spontaneous Slowing of AF Rotor (CL 140 ms) On Transition to LA Tachycardia (CL 206 ms) in 45 year old man with paroxysmal AF. A: ECG and CS electrograms for AF and AT. B: FIRM map of AF (right panel) showing counterclockwise rotor (CL ~140 ms) and surrounding disorganization. FIRM map of AT (left panel), showing counterclockwise reentry (CL ~200 ms) at this location. C: Site of shared AF/AT mechanism in LA which terminated to sinus rhythm by ablation at this shared LA site alone.

Fig. 4.

Shared focal source contributing to AF and causing AT, at a site of low voltage in 60 year old male with paroxysmal AF. A: RA FIRM map of AF showing lateral rotor and septal focal source. B: Two concurrent localized sources in FIRM movie. C: Spontaneous AT shows focal activation from same septal RA site. D: Heat map of voltages shows lower voltage at this shared AF-AT site than surrounding sites.

Fig. 5. Anatomy of shared AF/AT sites on a schematic of both atria. Arrows indicate reentrant AT, stars indicate focal AT, curved arrow shows CTI flutter (atrial shell image modified from Kalman et al., Lancet 2012 with permission).

Table 1

Patient characteristics.

<i>Demographics (n=26)</i>	
Age (years)	61.8 ± 12.7
Hypertension	17 (65%)
Diabetes Mellitus	4 (15%)
Hyperlipidemia	12 (46%)
Obstructive Sleep Apnea	13 (50%)
Congestive Heart Failure	5 (19%)
Left ventricular ejection fraction (%)	57.7 ± 12.9
Left atrial diameter (mm)	42.2 ± 6.2
CHADS2 Score	1.9 ± 1.5
<i>AF characteristics</i>	
Persistent/paroxysmal AF	10/16
<i>Procedure characteristics</i>	
FIRM ablation	26/26
Pulmonary vein isolation	15/26
Cavotricuspid isthmus line	7/26
Mitral line	1/26